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The state of the art of chronic spontaneous urticaria in Italy

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ABSTRACT

Objective: To assess the clinical status of chronic spontaneous urticaria (CSU) and to understand treatment approaches in Italy through both specialists who treat CSU (dermatologists and allergy specialists) and CSU patients' experience.

Design: Multicenter survey

Setting: Online structured questionnaires (one for physicians and one for patients)

Participants: Physicians and patients in Italy

Interventions: None

Primary/secondary outcomes: Physician and patient attitudes/experiences

Results: Survey results from 160 allergy and 160 dermatology specialists show that specialists see a median of 40 (interquartile range [IQR] 20–80) patients/year. While most specialists (56%) know the CSU guidelines, only 27% use them regularly (36% of allergy specialists vs 18% of dermatologists). This is reflected in treatment choices: while 77.2% of specialists choose standard-dose, non-sedating antihistamines as first-line treatment, only 64.4% would select up-dosing for second-line. Subsequent-line treatments differ widely, often not conforming to the guidelines. The diaries from 1385 patients highlight that, regardless of treatment regimen, 29.4% of currently treated patients are refractory to therapy. Specialists aim to resolve symptoms, and only 7.8% report improving quality of life (QoL) as a priority. Knowledge and use of tools for assessing disease activity are unsatisfactory: 46.9% of specialists do not know the Urticaria Activity Score and only 16.6% are familiar with and utilize it. Overall, 537 patients with CSU were surveyed (median age 37 years, IQR 30–46; 44.3% male;

median disease duration 5 years, IQR 3–20). Approximately 62% confirm that CSU negatively impacts their QoL. Patients also complain of difficulties in getting information and support: less than 5% of medical centers provide patient support services.

Conclusions: In Italy, the gap between guideline-based care and QoL-related needs in CSU patients affects treatment satisfaction. This information could be used to improve the management of CSU in Italy.

Article summary

Strengths and limitations of this study

- A strength of the study is the representative sample of both specialists who treat CSU and patients with CSU in Italy, giving insight into the management of this condition from dermatologists' and allergists' experience
- Limitations include those inherent to the survey/questionnaire format such as subjective bias

INTRODUCTION

Urticaria is a disease characterized by the spontaneous development of wheals (papules or plaques), angioedema or both, that is associated with itching, a burning sensation and/or pain.[1] Wheals typically resolve within several hours to a day with no residual appearance. Angioedema is also sudden in appearance, but the swelling of the subcutaneous (lower dermis and subcutis) or submucosal tissues is associated with pain rather than itching, and a slower resolution than that for wheals, generally up to 72 hours.[1]

Most cases of urticaria tend to be acute (<6 weeks); however, urticaria lasting for 6 weeks or more is considered chronic and is further classified as two subtypes, chronic spontaneous urticaria (CSU) and inducible urticaria. The cause of the spontaneous appearance of daily or episodic wheals, with or without angioedema, in CSU can be known or unknown,[1] and symptoms can last for more than 5 years.[2, 3]

An estimated 0.5–1% of the population, including children and adults, may be affected by CSU.[2, 4] CSU is associated with a large societal burden, an impact on patients' personal life, reduced work performance and direct and indirect healthcare costs.[5]

The care of patients with CSU is challenging because of the frequent lack of an underlying cause, the unpredictable disease course, the high disease burden, and the often limited efficacy of approved therapies.[5] Furthermore, CSU can have a significant impact on the patient's quality of life (QoL), and patients with CSU often experience depression and anxiety related to the disease.[4, 6-8] Failed attempts to treat long-term symptoms can often lead to frustration on the part of both the patient and the physician,[5] and patients with long-term unresolved symptoms often present to a

number of physicians in varying specialties in an attempt to seek relief.[4]

Data regarding CSU in Italy are currently limited. This survey aimed to assess the clinical status of CSU in Italy from the perspective of specialists who treat CSU (dermatologists and allergy specialists) and patients who have the disease. Both the specialists' therapeutic approach and the patients' experiences were assessed, with a focus on potential barriers to diagnosis and treatment that patients with CSU in Italy may experience.

METHODS

Study design

This multicenter Italian survey comprised two questionnaires, one for physicians and one for patients with CSU. Only data from patients and physicians who accepted to be interviewed were collected. Survey results were collated and analyzed by an independent market research company (Stethos Marketing Research, Milan, Italy) and stratified according to geographical area and hospital/center size. Due to the qualitative nature of these surveys, no inferential analyses were performed.

The research was conducted in conformity with the Code of Conduct 2014 of the European Pharmaceutical Market Research association (EphMRA).

Physician survey

Data were collected from a sample of physicians, specifically specialists in dermatology or allergy, to assess their diagnostic-therapeutic approach to CSU. Physicians and centers were selected from a proprietary database of Stethos Marketing Research. In order to obtain a good level of confidence, 320 physicians from across Italy who were directly involved in the diagnosis and treatment of CSU were enrolled.

Physicians were asked to complete a survey exploring their approach to the management of CSU and also provided completed patients diaries. The survey, consisting of 29 questions, was conducted online using Computer-Assisted Web Interviews (C.A.W.I.) with self-administered structured questions in Italian. The questions explored the characteristics of patients with CSU seen in the clinical practice, the treatments used and the criteria for their choice, the perceived goals and main drawbacks of therapy and the level of knowledge of existing guidelines. The specialists completed online Web Patient Diaries for the last five CSU patients examined during the study reference period. The objective was to collect at least 1000 patient diaries to allow for a robust dataset. This sample of interviewees was to be representative of the population of the CSU specialists in Italy, with a maximum margin of error of ±5.3 and a 95% confidence interval (CI).

Patient survey

The patient sample was targeted to ensure a good distribution by geographical area and size of the treating hospital. This was achieved by ranking the centers by the number of CSU patients being treated: the centers with the highest number of patients were selected. A random sample of patients with CSU being treated in each of these centers was asked to participate in the survey, before/after a routine assessment at the dermatology/allergy department. Planned enrolment was about 500 patients with CSU (an average of 4–5 patients from each center). This sample of respondents to the patient survey was to be representative of the population of patients with CSU in Italy (0.5–1% of the Italian population), with a maximum margin of error of ±4.2 and a 95% CI.

The patient surveys were self-administered via a C.A.W.I. system platform, and comprised of 46 questions, including those where the respondents could provide

demographic details, disease characteristics and disease history, rate their QoL and their treatment satisfaction. To investigate the journey of a patient with CSU arriving at a dermatology/allergy hospital center, the survey questions aimed to identify the steps followed and the possible barriers encountered during the diagnostic and therapeutic pathway, and to assess the impact of the condition on the patients' QoL.

RESULTS

Specialist perspective

Demographic distribution of the specialists

In total, 320 (160 allergy and 160 dermatology specialists) physicians from 194 centers in Northern (35.1%), Central (26.8%) and Southern (38.1%) Italy participated in the survey, and collected 1385 online patient diaries. The data were collected from January 29, 2014 to April 7, 2014. The distribution of allergy and dermatology specialists working in hospital practice (18.8% vs 16.9%), both hospital and private practice (49.4% vs 40.0%), or private practice only (31.9% vs 43.1%), was similar between groups.

Patients managed by the specialists

The allergy and dermatology specialists reported managing a median of 40 (IQR 20–80) patients with CSU annually, among whom the incidence of angioedema was 35.9%. Almost half of the patients treated by these specialists (as assessed by evaluation of the 1385 patient diaries) were considered to have severe disease (n=681; 49.2%); the remaining patients were considered to have mild CSU (n=704; 50.8%). The distribution of patients in relation to disease severity did not change when the patient data from allergy and dermatology specialists (n=662 and n=723, respectively) were assessed

separately. The number and frequency of the patients symptoms were considered the key parameters for determining disease severity by both specialist groups, while the impact of CSU on patients QoL, the efficacy of the therapy and the comorbidities were deemed relevant by fewer specialists.

Among all the patients managed by the surveyed specialists, 39.3% had symptoms that appeared frequently and regularly; more patients with severe disease reported frequent and regular symptoms (49.0%). The majority of patients (71.7%) had frequent symptoms, with or without regularity. In patients with mild disease the symptoms tended to manifest in an unpredictable manner (Figure 1).

Patient referral and disease diagnosis

Data from the patient diaries showed that patients were commonly referred to a CSU specialist by a general practitioner (32.6%), after visitation to the emergency department (21.2%), or, in 20.9% of patients, they sought a specialist themselves when symptoms appeared. Some patients were referred to the allergy and dermatology specialists by other specialists, including dermatologists (11.0%), allergy specialists (6.0%), or other specialists (2.2%). It was unknown how the remaining patients (6.2%) were referred to the specialist. The first symptoms referred by patients to specialists were hives (47.9%), itching (47.7%), urticaria (37.5%) and angioedema (24.8%). The latter was most frequently referred by severe patients (33.2%) compared to mild patients (15.9%). The diagnosis of CSU was established by a dermatologist in 67.3% of cases (either the surveyed [46.0%] or previous [21.3%] dermatologist) and an allergy specialist in 22.3% of cases (either the surveyed [14.4%] or previous [7.9%] allergy specialist). General practitioners (10.0%) or other specialists (0.4%) were involved markedly less frequently in diagnosing CSU. Among the 320 specialists surveyed, the diagnosis of CSU was

established an average of 7 months (median of 4 months, IQR 2–10.5) after the onset of the first symptoms in patients.

Symptomatic treatment of chronic spontaneous urticaria

When queried about the "ideal sequence" of symptomatic treatment for a patient with CSU (reflecting the approved indications at the time of the survey, in 2014), the majority (77.2%) of all specialists surveyed indicated that a standard dose of a non-sedating antihistamine was ideal as first-line treatment, while an increased-dose (<4 times the standard dose) non-sedating antihistamine was selected by 64.4% of specialists for second-line treatment. While 45.1% of specialists chose an increased-dose non-sedating antihistamine in combination with a leukotriene antagonist (LTRA)/H_2-antihistamine as third-line treatment, 36.1% indicated an increased-dose non-sedating antihistamine in combination with steroids would be an ideal third-line treatment; 30.9% of physicians indicated that they would reserve the latter as fourth-line treatment. 54.9% chose an increased-dose non-sedating antihistamine in combination with cyclosporine as a preferred fifth- or sixth-line treatment.

For the 1157 (83.5%) patients with CSU seen by the allergy and dermatology specialists who were receiving treatment at the time of the survey, the majority received a standard dose non-sedating H_1-antihistamine or increased-dose non-sedating H_1-antihistamine (Figure 2a). Fewer patients were receiving an increased-dose non-sedating antihistamine either in combination with steroids, cyclosporine, H_2-antihistamine, LTRA/H_2-antihistamine or LTRA (Figure 2a).

Comparing patients who had mild and severe disease, increased disease severity was associated with more complex treatment regimens, predominantly increased-dose non-sedating antihistamine in combination with steroids or cyclosporine. While standard-

dose non-sedating antihistamines were used as treatment for patients with mild disease, markedly fewer patients with severe disease received this treatment (Figure 2b).

Refractory chronic spontaneous urticaria

Regardless of the type of treatment received, 29.4% of all the patients with CSU currently treated were refractory to their therapy when the survey was conducted. Examining unresponsiveness for each current treatment showed that increased treatment was associated with increasing rates of unresponsiveness/disease severity (Figure 3).

Treatment goals

For the specialists surveyed, the main goal of treatment was to reduce the symptoms of CSU, in particular itching (87.8%) and hives (46.2%). Only 7.8% of physicians reported improving QoL as a priority, although 15.0% did consider this a second priority. Generally there were no significant differences between allergy and dermatology specialists for treatment goals, except for a greater tendency of allergy specialists to report improvement of QoL as a second treatment goal (15.0%) compared with dermatologists (10.0%).

Treatment guidelines

Among the 320 specialists surveyed, 56% were familiar with and used CSU guidelines; however, only 27% did so regularly. Compared with dermatologists, allergy specialists were twice as likely to regularly use guidelines (18% vs 36%, respectively) and knew of the CSU guidelines (45% vs 73%, respectively). Of those 189 specialists who confirmed that they knew CSU guidelines, the most commonly known were those by the European Academy of Allergy and Clinical Immunology (EAACI; 32.8%) and Associazione Allergologi Immunologi Territoriali e Ospedalieri (AAITO; 21.7%).[1, 9]

Disease activity assessment

Regarding the main scales used worldwide to assess and define the level of severity of CSU, 46.9% of the specialists did not know the Urticaria Activity Score (UAS). Although 36.6% knew of the scale, only 16.6% were familiar with and utilized the scale. Furthermore, 51.6% of the specialists did not know the UAS 7 days (UAS7), which uses the sum of the daily UAS scores to supply a weekly UAS value, and only 6.6% used it. Finally, only 16.9% of the specialists surveyed were familiar with and utilized the Chronic Urticaria Quality of Life Questionnaire (CU-QoL).

There were no significant differences between the allergy and dermatology specialists in the familiarity and utilization of the UAS/UAS7 scales; the proportion of specialists who were unfamiliar with the UAS (41.9% and 51.9%, respectively) and UAS7 (48.1% and 55.0%, respectively) scales was high in both groups.

Complexity of disease diagnosis

When all the specialists were asked to rate the level of complexity in diagnosing CSU on a scale of 1 to 10, where 1 = not at all complex to 10 = extremely complex, 40% considered that there was a high level of complexity (≥8) in diagnosing CSU. When the 210 specialists who rated the level of complexity as >5 were queried about the elements that increase the complexity of diagnosing CSU, over half (55.2%) chose 'several tests to diagnose CSU', while 44.3% responded that it was due to 'the great difficulty in identifying the cause of the pathology'; there were no significant differences in the responses to this questions between the allergy and dermatology specialists.

A quarter of all specialists surveyed (n = 83) revealed that they consult with another specialist, and there is generally a high level of collaboration between allergy and

dermatology specialists. In 95.3% of cases, the dermatologists requesting a colleague's opinion will turn to an allergy specialist, whereas 62.5% of allergy specialists will request a dermatologist's opinion and 70.0% the opinion of another allergy specialist.

Patient perspective

Demographic and disease characteristics

In total, 537 patient surveys were conducted between May 6, 2014 to June 12, 2014. The patients who responded to the survey (55.7% female) had mean age of 39 years (median 37 years, IQR 30–46). Mean and median ages were similar between men (mean 39 years; median 38, IQR 31–46) and women (mean 39; median 37 years, IQR 29–46). Almost 84% of respondents were aged 50 years or under (Table 1).

Table 1. Baseline demographic characteristics of patients with chronic spontaneous urticarial (CSU).

Characteristic or demographic	Patient survey respondents (N=537)
Gender, n (% patients)	
Female	299 (55.7)
Male	238 (44.3)
Age group, n (% patients)	
≤30 years	139 (25.9)
31–40 years	175 (32.6)
41–50 years	135 (25.1)
51–60 years	66 (12.3)
>60 years	22 (4.1)
Geographical region, n (% patients)	
North-West	141 (26.3)
North-East	61 (11.4)
Centre	106 (19.7)
South	229 (42.6)
Disease severity, n (% patients)	
Mild	120 (22.3)
Moderate	323 (60.1)
Severe	56 (10.4)

At the time of the survey, patients had an average disease duration of 13 years (median 5 years, IQR 3–20) and 45.6% of patients had lived with the disease for 2–5 years (Table 1). The majority of patients surveyed had moderate disease (Table 1).

Impact of chronic spontaneous urticaria on quality of life

Almost two-thirds (61.6%) of patient respondents indicated that their CSU had a negative impact on their QoL, with a rating of 4–6 (where 1 = no impact on QoL to 6 = significant impact on QoL), while only 4.3% reported the CSU had no influence on their QoL. The frequency of patients rating the impact of CSU on their QoL as ≥4 to 6 varied with disease severity, from a minimum of 35.8% of patients with mild disease to 70.0% and 80.4% of patients with moderate and severe disease, respectively. One third (33.9%) of patients with severe CSU rated the level of disease influence on their QoL as 6 (significant), compared with 5.9% and 3.3% of patients with moderate and severe disease, respectively.

The most frequent reasons cited for decreased QoL were social discomfort/aesthetic issues (33.5%) and itching/skin discomfort (28.9%; Figure 4). The frequency of reasons cited as negatively influencing QoL did not vary greatly when the patients were stratified by disease severity; however, a greater number of patients with severe CSU than those with moderate or mild disease reported stress/anxiety/irritation/insomnia (12.5% vs 5.9% and 0.8%) and negative impact on working life (7.1% vs 0.9% and 0.8%) as influencing their QoL.

Choice of physician

One third of patients (35.2%) had seen other physicians prior to their current one. On average patients had previously changed at least two specialists. The most frequent

reason for changing physicians was “dissatisfaction with the medical staff of the previous facility” (23.3%), followed by “the current center/physician is closer to where I live” (20.6%), “previous physicians were not able to find the right therapy” (19.6%), “previous physicians took too long to diagnose my disease” (18.0%), “innovative therapies that I couldn’t access before are available in the new center” (14.8%), and “other” (3.7%).

The number of specialists that the patient changed in the past did not vary significantly when the sample was stratified by disease severity.

Provision of support services and patient information channels

Less than 5% of respondents indicated that the medical center that they attended provided patient support services. When support services were provided, these included support for families, psychological support and use of specific lotions.

Hard copy disease-related material (e.g., brochures about CSU) was distributed to 34.6% of respondents when they attended their care facility. The types of brochures provided included information/advice about: diet and lifestyle (65.1%); pathology evolution and symptoms (50.5%); general CSU information (45.7%); therapies (38.7%); patient diaries (21.0%); and modes of administration (19.9%).

When asked about the communication channels they used to access updates or information about their disease, 67.7% of patients responded that they had obtained information from internet sources at least once, including CSU-related websites, general internet searches, and online forums, while 41.3% asked a dermatologist. The types of channels through which patients received their information are summarized in Table 2.

Table 2. Sources of disease information accessed by the patients with chronic spontaneous urticaria (CSU) who responded to the survey.

Source of information, n (% of patients)	Patient survey respondents (N=537)
Dermatologist	222 (41.3)
Online forums	158 (29.4)
Internet in general	137 (25.5)
Printed documentation	133 (24.8)
CSU-dedicated website	69 (12.8)
Conferences	63 (11.7)
Hospital nurses	38 (7.1)
Other	18 (3.4)
Patient association	10 (1.9)
None	60 (11.2)

DISCUSSION

Based on the survey results, the specialists who treat CSU throughout Italy are managing a median 40 patients (IQR 20–80) each year. About half of CSU patients seen by allergy and dermatology specialists have mild CSU whereas the other half have severe disease. However, due to high proportion of specialists of both groups who were not familiar with the UAS and UAS7 scales, the classification of disease severity may not have been sufficiently objective. The importance of this clinical tool has to be stressed both for initial disease severity grading and for monitoring treatment efficacy.

A third of patients are referred to a CSU specialist by a general practitioner, and a fifth by emergency department staff or self-referral at symptom onset. Notably, more dermatologists than allergy specialists established the diagnosis of CSU. This may simply reflect the fact that, in Italy, dermatology specialists outnumber allergy specialists by three to one, therefore dermatologists are more accessible to patients than allergy specialists. General practitioners were only involved in the diagnosis of 10% of patients with CSU, emphasizing the complexity of diagnosing the disease and the need

of referral to a specialist to establish a diagnosis. Overall, diagnosis was established an average of 7 months (median of 4 months, IQR 2–10.5) after the appearance of the first symptoms, although time to diagnosis was increased with disease severity (up to 13 months), possibly because a more accurate medical history has to be collected from each patient. Highlighting the complexity of the disease itself, 40% of specialists surveyed felt that CSU diagnosis was complex and the difficulty in identifying the cause of the pathology and the multiplicity of tests available for diagnosis were listed as factors contributing to the level of complexity in disease diagnosis. On the other hand the international guidelines strongly recommend only very limited routine diagnostic evaluations in CSU, in order to reduce the number of diagnostic tests.[1]

For most of the allergy and dermatology specialists, the ideal sequence of treatment, at the time of the survey, would be a standard and an increased dose of a non-sedating antihistamine as first-line and second-line treatment, respectively. For third-line treatment for non-responders, specialists tended to favor treatment with an increased dose non-sedating antihistamine in combination with a LTRA and an H_2-antihistamine, or an increased dose non-sedating antihistamine in combination with a steroid or cyclosporine, a regimen especially preferred in more severe disease. Nevertheless, regardless of treatment regimen, over a quarter of all patients with CSU were refractory to the therapy they were receiving, and even complex/aggressive treatment regimens failed to resolve symptoms in almost half of the patients with severe disease. It should be noted that, at the time of the survey, a new therapeutic option was not yet authorized for CSU treatment. However, since then the approach to patients with refractory CSU has changed: the current EAACI/GA_2LEN/EDF/WAO guidelines describe omalizumab as a 3rd line treatment for urticaria and the Italian regulatory authorities recommend to use omalizumab when patients do not respond to standard dosage of non-sedating

antihistamine.[1]

Moreover, data suggest that continuous therapy is associated to improved outcomes in terms of QoL.[5] However, this is not always reflected in real-life: a survey in patients with CSU in Germany and France showed that 78% of patients were taking medication for their CSU, but only 33% of these were taking it regularly for symptom prevention.[10]

For the specialists surveyed, the main goal of CSU treatment was key symptom resolution (itching and hives) and few considered improving QoL a priority. Importantly, the updated EAACI/GA$_2$LEN/EDF/WAO guidelines strongly recommend complete symptom control, as safely as possible, to be the goal of treatment.[1] Appropriate management of CSU requires evidence-based guidance; however, only half of the specialists surveyed (more allergy specialists than dermatologists) knew of and used any of the CSU guidelines available, with allergy specialists twice as likely as dermatologists to use guidelines. Similarly, there was a gap in the knowledge of the specialists regarding the main scales used to assess disease activity, with only approximately half of the surveyed specialists acknowledging familiarity with the UAS and UAS7, and only one-sixth acknowledging familiarity with and utilized the CU-QoL questionnaire. The 2014 EAACI/GA$_2$LEN/EDF/WAO guidelines provide a strong recommendation that disease activity should be assessed in clinical care using the UAS7, and that the CU-QoL is one of the validated instruments for assessing QoL impairment and for monitoring disease activity.[1]

Among patients surveyed across Italy, the prevalence of CSU has been found to be about the same in women and in men, unlike reports from other countries [3, 11]. Similar to patients with CSU in other countries,[12] about two-thirds of patients

reported that CSU had a negative impact on their QoL, affecting both their personal and professional life, and the frequency and level of impact increased with disease severity. More patients with severe disease than those with moderate of mild disease cited stress/anxiety/irritation/insomnia and negative impact on working life as impacting QoL.

In their efforts to obtain symptom relief, over a third of patients had on average consulted two previous physicians. Surprisingly, the number of specialists changed did not vary significantly when stratified by disease severity. The most common reason for switching providers was dissatisfaction with medical staff. Attending multiple medical centers due to dissatisfaction with treatment and reports of reduced quality of life are in accordance with existing literature in patients with CSU.[4, 6-8] A patient survey conducted in Germany and France also reiterated the impact CSU has on QoL and lack of satisfaction with physician care,[12] with patients indicating they were only "somewhat satisfied" with the care they were receiving. Satisfaction with treatment increased if the physician discussed the impact of CSU on emotions with their patient.

There appear to be a mismatch between patients with CSU and specialists as, while two third of the patients reported CSU affecting their QoL, only 8% of specialists considered improving QoL as a priority. Our results suggest that there is a need for specialists to routinely use the CU-QoL, in order to assess how patients are affected by the disease, and the UAS to monitor the disease and provide the most appropriate treatment. It is therefore important for specialists to focus their attention on the burden and the unmet needs of CSU and establishing more satisfying treatment schemes.

Furthermore, most patients (>95%) did not have patient support services available to them at their medical center.

The limitations of the present study include those inherent in the survey/questionnaire format. Although the questionnaires were designed to minimize bias, there is always a subjective element remaining (e.g. respondents tend to avoid scoring at the end of scales and answer in a way they perceive to be desired by the investigator/be more socially acceptable).[13] A strength of the study is that, by selecting a representative sample of both patients with CSU and of specialists involved in the treatment of CSU in Italy, it provides a snapshot of the management of this condition from both perspectives, thereby highlighting current gaps in guideline-based care and unmet patient needs.

CONCLUSIONS

In general, patients in Italy with CSU are similar to patients with CSU in other countries. However, there are some gaps in the care of these patients resulting in treatment dissatisfaction and a decreased QoL. These results should be used to improve the treatment of patients with CSU in Italy, in particular by reinforcing the knowledge of the available tools, such as the UAS and CU-QoL questionnaires, which can be used to assist specialists in treating patients with CSU.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Author contributions

MR and NR were responsible for conception and design of the survey. MR was responsible for the acquisition of data; MR and NR had full access to the final data and performed the analysis. MR, NR and OR contributed to data interpretation, to the drafting and critical revision of the manuscript. All authors approved the final version and have final responsibility for content.

Medical writing, editorial, and other assistance

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Competing interests

Oliviero Rossi has been consultant and speaker for Meda, Novartis, MSD, Menarini in the last five years.

Marco Rimoldi is a partner of Stethos Srl and holds shares of this Company. Stethos Srl collaborates with Novartis Farma Italy on several market researches.

Nadia Rota is employee of Novartis Farma, Italy.

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Compliance with ethics guidelines

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Data Sharing

No additional unpublished data are available

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Figure legends

Figure 1. Frequency and regularity of symptoms of chronic spontaneous urticaria in patients with mild disease as reported by their physicians.

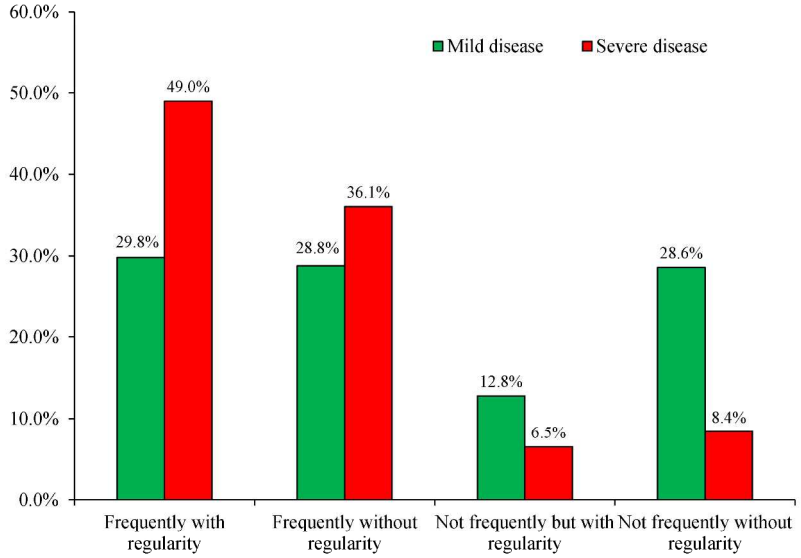
Figure 2. (a) Therapies received by the 1157 patients with chronic spontaneous urticaria currently treated by 320 specialists surveyed and (b) therapies received by patients with severe and mild forms of the disease.

H2AH, H_2-antihistamine; LTRA, leukotriene receptor antagonist; nsAH, non-sedating antihistamine.

Figure 3. Rates of refractory disease according to current treatment and disease severity.

H2AH, H_2-antihistamine; LTRA, leukotriene receptor antagonist; nsAH, non-sedating antihistamine.

Figure 4. The most frequent reasons for decreased quality of life as reported in the survey of patients with chronic spontaneous urticaria (N=357). Reasons shown are the answers to question 29 of the survey "What aspect of your disease would you indicate as the most impactful on your life?"



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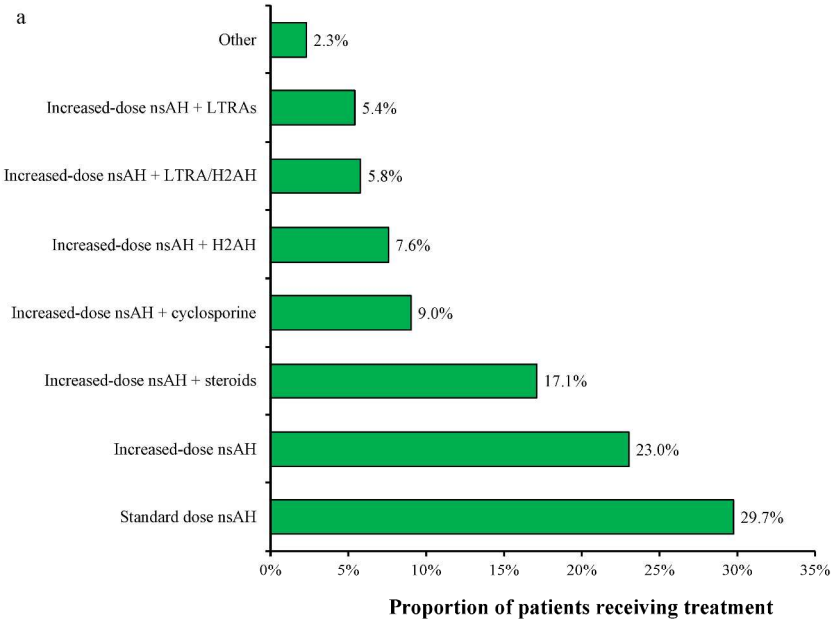

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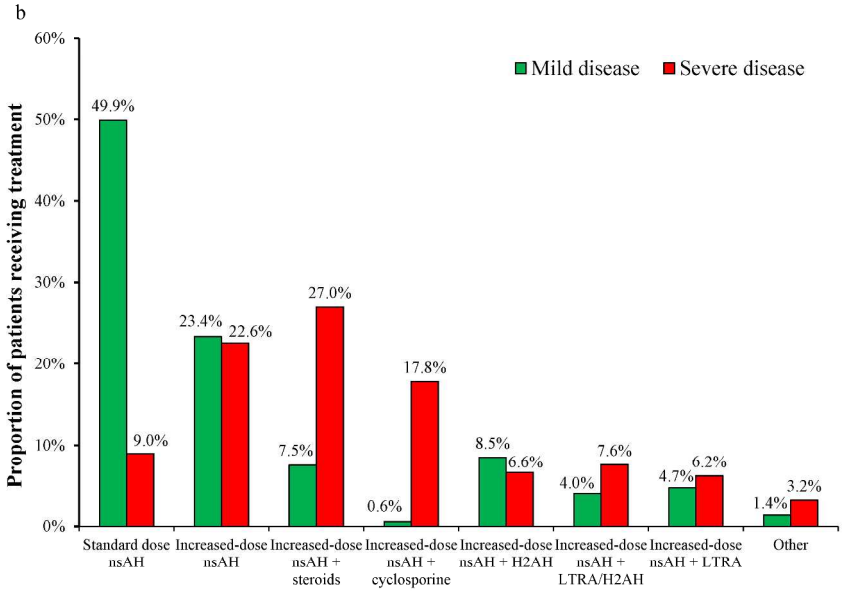

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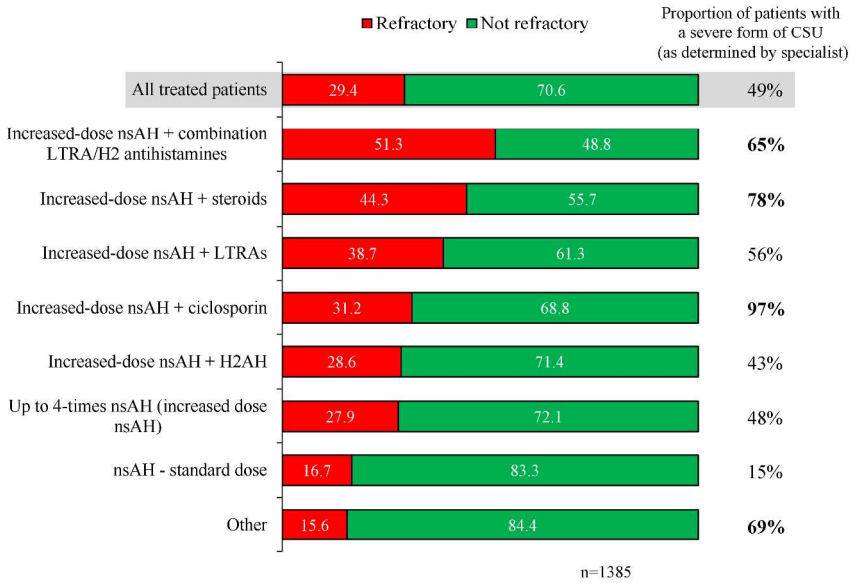

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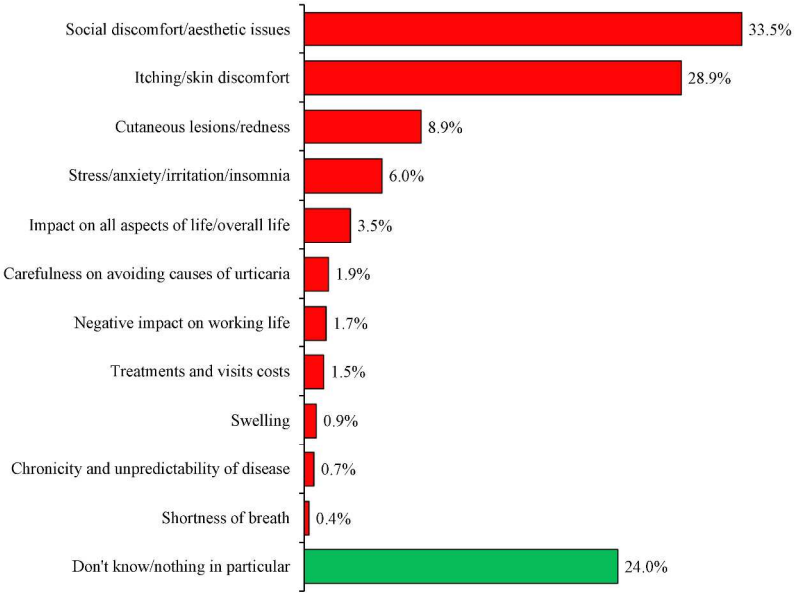

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The state of the art of chronic spontaneous urticaria in Italy: a multicenter survey to evaluate physicians' and patients' perspective

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The state of the art of chronic spontaneous urticaria in Italy: a multicenter survey to evaluate physicians' and patients' perspective

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ABSTRACT

Objective: To assess the clinical status of chronic spontaneous urticaria (CSU) and understand treatment approaches in Italy through both specialists who treat CSU (dermatologists and allergy specialists) and CSU patients' experience.

Design: Multicenter survey

Setting: Online structured questionnaires (one for physicians and one for patients)

Participants: Physicians and patients with CSU in Italy

Interventions: None

Primary/secondary outcomes: Physician and patient attitudes/experiences

Results: Survey results from 160 allergy and 160 dermatology specialists show that specialists see a median of 40 (interquartile range [IQR] 20–80) patients with CSU/year. While most specialists (56%) know the CSU guidelines, only 27% use them regularly (36% of allergy specialists vs 18% of dermatologists). This is reflected in treatment choices with differences between physicians who use guidelines regularly and those who do not: 91.6% versus 71.7% choose standard-dose, non-sedating antihistamines (nsAH) as first-line treatment; 85.9% versus 56.0% select up-dosing for second-line; and 65.3% versus 37.2% add leukotriene receptor antagonists (LTRA) or H_2-antihistamines as third-line treatment. The diaries from 1385 patients highlight that, regardless of treatment regimen, 29.4% of currently treated patients are refractory to therapy. Specialists aim to resolve symptoms and only 7.8% report improving quality of life (QoL) as a priority. Only 16.6% of specialists are familiar with and utilize the

Urticaria Activity Score while 46.9% do not know it. Overall, 537 patients with CSU were surveyed (median age 37 years, IQR 30–46; 44.3% male; median disease duration 5 years, IQR 3–20). Approximately 62% confirm that CSU negatively impacts their QoL. Patients also complain of difficulties in getting information and support: less than 5% of medical centers provide patient support services.

Conclusions: In Italy, the gap between guideline-based care and QoL-related needs in CSU patients affects treatment satisfaction. This information could be used to improve the management of CSU in Italy.

Article summary

Strengths and limitations of this study

- A strength of the study is the representative sample of both specialists who treat CSU and patients with CSU in Italy, giving insight into the management of this condition from dermatologists' and allergy specialists' experience
- Both CSU specialists and patients are represented, with a maximum margin of error of ±5.3% (95% confidence interval [CI]) and a maximum margin of error of ±4.2% (95% CI), respectively
- The conclusions drawn from the clinicians' perspective are supported by the collection of data from 1385 patient diaries
- The methodology minimizes bias because the physician survey was conducted online, without the involvement of an interviewer; the physicians were

responsible for compiling the survey and the patient diaries autonomously.

- Limitations include those inherent to the survey/questionnaire format, such as subjective bias

INTRODUCTION

Urticaria is a disease characterized by the spontaneous development of wheals (papules or plaques) that are associated with itching, a burning sensation and/or pain; in some cases they are also associated with angioedema. [1] Wheals typically resolve within several hours to a day with no residual appearance. Angioedema is also sudden in appearance, but the swelling of the subcutaneous (lower dermis and subcutis) or submucosal tissues is associated with pain rather than itching, and a slower resolution than that for wheals, generally up to 72 hours.[1]

Most cases of urticaria tend to be acute (<6 weeks); however, urticaria lasting for 6 weeks or more is considered chronic and is further classified as two subtypes, chronic spontaneous urticaria (CSU) and inducible urticaria. The cause of the spontaneous appearance of daily or episodic wheals in CSU, with or without angioedema, can be known or unknown,[1] and symptoms can last for more than 5 years.[2 3]

An estimated 0.5–1% of the population, including children and adults, may be affected by CSU.[2 4] CSU is associated with a large societal burden, an impact on patients' personal life, reduced work performance and direct and indirect healthcare costs.[5]

The care of patients with CSU is challenging due to inability to identify the underlying

cause, the unpredictable disease course, the high disease burden, and the often limited efficacy of approved therapies.[5] Furthermore, CSU can have a significant impact on the patient's quality of life (QoL), and patients with CSU often experience depression and anxiety related to the disease.[4 6-8] Failed attempts to treat long-term symptoms can often lead to frustration on the part of both the patient and the physician,[5] and patients with long-term unresolved symptoms often present to a number of physicians in varying specialties in an attempt to seek relief.[4]

Data regarding CSU in Italy are currently limited. This survey aimed to assess the clinical status of CSU in Italy from the perspective of specialists who treat CSU (dermatologists and allergy specialists) and patients who have the disease. Both the specialists' therapeutic approach and the patients' experiences were assessed, with a focus on potential barriers to diagnosis and treatment that patients with CSU in Italy may experience.

METHODS

Study design

This multicenter Italian survey comprised two questionnaires, one for physicians and one for patients with CSU. Only data from patients and physicians who accepted to be interviewed were collected. The survey was designed by an independent market research company (Stethos Marketing Research, Milan, Italy) and was tested with pilot interviews to specialists. Survey results were also collected and analyzed by Stethos Marketing Research and stratified according to geographical area and hospital/center size. Due to the qualitative nature of these surveys, no inferential analyses were

performed.

The research was conducted in conformity with the Code of Conduct 2014 of the European Pharmaceutical Market Research Association (EphMRA).

Physician survey

Data were collected from a sample of physicians, specifically specialists in dermatology or allergy, to assess their diagnostic-therapeutic approach to CSU. Physicians and centers were selected from a proprietary database of Stethos Marketing Research. In order to obtain a good level of confidence, 320 physicians – 160 dermatologists and 160 allergy specialists – from across Italy who were directly involved in the diagnosis and treatment of CSU were enrolled.

Physicians were asked to complete a survey exploring their approach to the management of CSU and also provided completed patient diaries. The survey, consisting of 28 questions, some of them with sub-questions (for a total of 37), was conducted online using a Computer-Assisted Web Interviewing (C.A.W.I.) platform with self-administered structured questions in Italian. The questions explored topics such as characteristics and records of patients with CSU seen in the clinical practice, patient management, treatments used, drivers for therapy, perceived goals, main drawbacks of therapy and the level of knowledge of existing guidelines (blank physician questionnaire forms, both in Italian and translated into English, are provided as Supplementary files 1 and 2, respectively). The specialists completed online Web Patient Diaries for the last five CSU patients examined during the study reference period. The objective was to collect at least 1000 patient diaries to allow for a robust

dataset including information about the diagnosis, the previous and current treatments and the frequency of visits (blank patient diaries forms, both in Italian and translated into English, are provided as Supplementary files 3 and 4, respectively). This sample of interviewees was to be representative of the population of the CSU specialists in Italy, with a maximum margin of error of ±5.3 and a 95% confidence interval (CI).

Patient survey

The patient sample was targeted to ensure a good distribution by geographical area and size of the treating hospital. This was achieved by ranking the centers by the number of CSU patients being treated: the centers with the highest number of patients were selected. A random sample of patients with CSU being treated in each of these centers was asked to participate in the survey, before/after a routine assessment at the dermatology/allergy department. Planned enrolment was about 500 patients with CSU (an average of 4–5 patients from each center). This sample of respondents to the patient survey was to be representative of the population of patients with CSU in Italy (0.5–1% of the Italian population), with a maximum margin of error of ±4.2 and a 95% CI.

The patient surveys were self-administered via a C.A.W.I. system platform, and comprised of 46 questions, some of them with sub-questions (for a total of 50), including those where the respondents could provide demographic details, disease characteristics and disease history, rate their QoL and their treatment satisfaction. To investigate the journey of a patient with CSU arriving at a dermatology/allergy hospital center, the survey questions aimed to identify the steps followed and the possible barriers encountered during the diagnostic and therapeutic pathway, and to assess the impact of the condition on the patients' QoL (blank patient questionnaire forms, both in

Italian and translated into English, are provided as Supplementary files 5 and 6, respectively).

RESULTS

Specialist perspective

Demographic distribution of specialists

In total, 320 physicians (160 allergy and 160 dermatology specialists) from 194 centers in Northern (35.1%), Central (26.8%) and Southern (38.1%) Italy participated in the survey, and collected 1385 online patient diaries. The data were collected from January 29, 2014 to April 7, 2014. The distribution of allergy and dermatology specialists working in hospital practice (18.8% vs 16.9%), both hospital and private practice (49.4% vs 40.0%), or private practice only (31.9% vs 43.1%), was similar between groups.

Patients managed by the specialists

The allergy and dermatology specialists reported managing a median of 40 (IQR 20–80) patients with CSU annually, among whom the incidence of angioedema was 35.9%. Almost half of the patients treated by these specialists were considered to have severe disease (n=681; 49.2%) while the remaining patients were considered to have mild CSU (n=704; 50.8%), as assessed by the evaluation of the 1385 patient diaries. The distribution of patients in relation to disease severity did not change when the patient data from allergy and dermatology specialists (n=662 and n=723, respectively) were assessed separately. The number and frequency of the patients symptoms were

considered the key parameters for determining disease severity by both specialist groups, while the impact of CSU on patients QoL, the efficacy of the therapy and the comorbidities were deemed relevant by fewer specialists.

Among all the patients managed by the surveyed specialists, 39.3% had symptoms that appeared frequently and regularly; more patients with severe disease reported frequent and regular symptoms (49.0%). The majority of patients (71.7%) had frequent symptoms, with or without regularity. In patients with mild disease the symptoms tended to manifest in an unpredictable manner (Figure 1).

Patient referral and disease diagnosis

Data from the patient diaries showed that patients were commonly referred to a CSU specialist by a general practitioner (32.6%), after visitation to the emergency department (21.2%), or, in 20.9% of patients, they sought a specialist themselves when symptoms appeared. Some patients were referred to the allergy and dermatology specialists by other specialists, including dermatologists (11.0%), allergy specialists (6.0%), or other specialists (2.2%). It was unknown how the remaining patients (6.2%) were referred to the specialist. The first symptoms reported by patients to specialists were hives (47.9%), itching (47.7%), urticaria (37.5%), and angioedema (24.8%). The latter was most frequently reported by severe patients (33.2%) compared with mild patients (15.9%). The diagnosis of CSU was established by a dermatologist in 67.3% of cases (either the surveyed [46.0%] or previous [21.3%] dermatologist) and an allergy specialist in 22.3% of cases (either the surveyed [14.4%] or previous [7.9%] allergy specialist). General practitioners (10.0%) or other specialists (0.4%) were involved markedly less frequently in diagnosing CSU. Among the 320 specialists surveyed, the diagnosis of CSU was

established an average of 7 months (median of 4 months, IQR 2–10.5) after the onset of the first symptoms in patients.

Specialists' knowledge of treatment guidelines

Among the 320 specialists surveyed, 56% were familiar with and used CSU guidelines, however, only 27% used them regularly. Compared with dermatologists, allergy specialists were twice as likely to regularly use guidelines (36% vs 18%) and more of them knew of the CSU guidelines (73% vs 45%; Figure 2a). A total of 189 specialists confirmed that they knew CSU guidelines; the guidelines that were most frequently mentioned as known (the relevant survey question was open-ended) were those by the European Academy of Allergy and Clinical Immunology (EAACI/GA$_2$LEN/EDF/WAO; 43.4%)[9] and Associazione Allergologi Immunologi Territoriali e Ospedalieri (AAITO; 21.7%).[10] The less-frequently known and used guidelines included those by Società Italiana di Dermatologia medica, chirurgica, estetica e delle Malattie Sessualmente Trasmesse (SIDeMaST; 4.2%[11]), British Society for Allergy and Clinical Immunology (BSACI; 2.6%[12]), and others (Figure 2b).

Symptomatic treatment of chronic spontaneous urticaria

When queried about the "ideal sequence" of symptomatic treatment for a patient with CSU (reflecting the approved indications at the time of the survey, in 2014), the majority (77.2%) of all specialists surveyed indicated that a standard dose of a non-sedating antihistamine (nsAH) was ideal as first-line treatment, while an increased-dose (<4 times the standard dose) nsAH was selected by 64.4% of specialists for second-line

treatment. While 45.1% of specialists chose an increased-dose nsAH in combination with a leukotriene antagonist (LTRA)/H_2-antihistamine as third-line treatment, 36.1% indicated an increased-dose nsAH in combination with steroids would be an ideal third-line treatment; 30.9% of physicians indicated that they would reserve the latter as fourth-line treatment. 54.9% chose an increased-dose nsAH in combination with cyclosporine as a preferred fifth- or sixth-line treatment.

Notably, knowledge and use of the CSU guidelines was reflected in treatment choices, with differences between physicians who use guidelines regularly and those who do not: 91.6% versus 71.7%, respectively, choose standard-dose nsAH as first-line treatment; 85.9% versus 56.0% select increased-dose nsAH for second-line; and 65.3% versus 37.2% add leukotriene receptor antagonists (LTRA) or H_2-antihistamines to increased-dose nsAH for third-line treatment. The combination of increased-dose nsAH and steroids was considered for third-line treatment by 26.0% versus 39.5% of physicians, respectively, and for fourth-line by 50.7% versus 24.2%; increased-dose nsAH in combination with cyclosporine was preferred for fifth-line by 62.0% versus 52.2% of specialists.

For the 1157 (83.5%) patients with CSU seen by the allergy and dermatology specialists who were receiving treatment at the time of the survey, the majority received a standard dose non-sedating H_1-antihistamine or increased-dose non-sedating H_1-antihistamine (Figure 3a). Fewer patients were receiving an increased-dose non-sedating antihistamine either in combination with steroids, cyclosporine, H_2-antihistamine, LTRA/H_2-antihistamine or LTRA (Figure 3a).

Comparing patients who had mild and severe disease, increased disease severity was

associated with more complex treatment regimens, predominantly increased-dose non-sedating antihistamine in combination with steroids or cyclosporine. While standard-dose non-sedating antihistamines were used as treatment for patients with mild disease, markedly fewer patients with severe disease received this treatment (Figure 3b).

Refractory chronic spontaneous urticaria

Regardless of the type of treatment received, 29.4% of all the patients with CSU currently treated were refractory to their therapy when the survey was conducted. Examining unresponsiveness for each current treatment showed that increased treatment was associated with increasing rates of unresponsiveness/disease severity (Figure 4).

Treatment goals

For the specialists surveyed, the main goal of treatment was to reduce the symptoms of CSU, in particular itching (87.8%) and hives (46.2%). Only 7.8% of physicians reported improving QoL as a priority, although 15.0% did consider this a second priority. Generally there were no significant differences between allergy and dermatology specialists for treatment goals, except for a greater tendency of allergy specialists to report improvement of QoL as a second treatment goal (15.0%) compared with dermatologists (10.0%).

Disease activity assessment

Of all the specialists, 46.9% did not know the Urticaria Activity Score (UAS). Although 36.6% knew of the scale, only 16.6% were familiar with and utilized the scale. Furthermore, 51.6% of the specialists did not know the UAS 7 days (UAS7), which uses

the sum of the daily UAS scores to supply a weekly UAS value, and only 6.6% used it. Finally, only 16.9% of the specialists surveyed were familiar with and utilized the Chronic Urticaria Quality of Life Questionnaire (CU-QoL).

There were no significant differences between the allergy and dermatology specialists in the familiarity and utilization of the UAS/UAS7 scales; the proportion of specialists who were unfamiliar with the UAS (41.9% and 51.9%, respectively) and UAS7 (48.1% and 55.0%, respectively) scales was high in both groups.

Complexity of disease diagnosis

When all the specialists were asked to rate the level of complexity in diagnosing CSU on a scale of 1 to 10 (1 = not at all complex; 10 = extremely complex), 40% considered that there was a high level of complexity (≥8) in diagnosing CSU. When the 210 specialists who rated the level of complexity as >5 were queried about the elements that increase the complexity of diagnosing CSU, over half (55.2%) chose 'several tests to diagnose CSU', while 44.3% responded that it was due to 'the great difficulty in identifying the cause of the pathology'; there were no significant differences in the responses to this questions between the allergy and dermatology specialists.

A quarter of all specialists surveyed (n = 83) revealed that they consult with another specialist, and there is generally a high level of collaboration between allergy and dermatology specialists. In 95.3% of cases, the dermatologists requesting a colleague's opinion will turn to an allergy specialist, whereas 62.5% of allergy specialists will request a dermatologist's opinion and 70.0% the opinion of another allergy specialist.

Patient perspective

Demographic and disease characteristics

In total, 537 patient surveys were conducted between May 6, 2014 to June 12, 2014. The patients who responded to the survey (55.7% female) had a mean age of 39 years (median 37 years, IQR 30–46). Mean and median ages were similar between men (mean 39 years; median 38, IQR 31–46) and women (mean 39; median 37 years, IQR 29–46). Almost 84% of respondents were aged 50 years or under (Table 1).

Table 1. Baseline demographic characteristics of patients with chronic spontaneous urticarial (CSU).

Characteristic or demographic	Patient survey respondents (N=537)
Gender, n (% patients)	
Female	299 (55.7)
Male	238 (44.3)
Age group, n (% patients)	
≤30 years	139 (25.9)
31–40 years	175 (32.6)
41–50 years	135 (25.1)
51–60 years	66 (12.3)
>60 years	22 (4.1)
Geographical region, n (% patients)	
North-West	141 (26.3)
North-East	61 (11.4)
Centre	106 (19.7)
South	229 (42.6)
Disease severity, n (% patients)	
Mild	120 (22.3)
Moderate	323 (60.1)
Severe	56 (10.4)

At the time of the survey, patients had an average disease duration of 13 years (median

5 years, IQR 3–20) and 45.6% of patients had lived with the disease for 2–5 years (Table 1). The majority of patients surveyed had moderate disease (Table 1).

Impact of chronic spontaneous urticaria on quality of life

Almost two-thirds (61.6%) of patient respondents indicated that their CSU had a negative impact on their QoL, with a rating of 4–6 (1 = no impact on QoL; 6 = significant impact on QoL), while only 4.3% reported the CSU had no influence on their QoL. The frequency of patients rating the impact of CSU on their QoL as ≥4 to 6 varied with disease severity, from a minimum of 35.8% of patients with mild disease to 70.0% and 80.4% of patients with moderate and severe disease, respectively. One third (33.9%) of patients with severe CSU rated the level of disease influence on their QoL as 6 (significant), compared with 5.9% and 3.3% of patients with moderate and severe disease, respectively.

The most frequent reasons cited for decreased QoL were social discomfort/aesthetic issues (33.5%) and itching/skin discomfort (28.9%; Figure 5). The frequency of reasons cited as negatively influencing QoL did not vary greatly when the patients were stratified by disease severity; however, a greater number of patients with severe CSU than those with moderate or mild disease reported stress/anxiety/irritation/insomnia (12.5% vs 5.9% and 0.8%) and negative impact on working life (7.1% vs 0.9% and 0.8%) as influencing their QoL.

Choice of physician

One third of patients (35.2%) had seen other physicians prior to their current one. On average patients had previously changed at least two specialists. The most frequent

reason for changing physicians was “dissatisfaction with the medical staff of the previous facility” (23.3%), followed by “the current center/physician is closer to where I live” (20.6%), “previous physicians were not able to find the right therapy” (19.6%), “previous physicians took too long to diagnose my disease” (18.0%), “innovative therapies that I couldn’t access before are available in the new center” (14.8%), and “other” (3.7%). The number of specialists that the patient changed in the past did not vary significantly when the sample was stratified by disease severity.

Provision of support services and patient information channels

Less than 5% of respondents indicated that the medical center that they attended provided patient support services. When support services were provided, these included support for families, psychological support and use of specific lotions.

Hard copy disease-related material (e.g., brochures about CSU) was distributed to 34.6% of respondents when they attended their care facility. The types of brochures provided included information/advice about: diet and lifestyle (65.1%), pathology evolution and symptoms (50.5%), general CSU information (45.7%), therapies (38.7%), patient diaries (21.0%), and modes of administration (19.9%).

When asked about the communication channels they used to access updates or information about their disease, 67.7% of patients responded that they had obtained information from internet sources at least once, including CSU-related websites, general internet searches, and online forums, while 41.3% asked a dermatologist. The types of channels through which patients received their information are summarized in Table 2.

Table 2. Sources of disease information accessed by the patients with chronic spontaneous urticaria (CSU) who responded to the survey.

Source of information, n (% of patients)	Patient survey respondents (N=537)
Dermatologist	222 (41.3)
Online forums	158 (29.4)
Internet in general	137 (25.5)
Printed documentation	133 (24.8)
CSU-dedicated website	69 (12.8)
Conferences	63 (11.7)
Hospital nurses	38 (7.1)
Other	18 (3.4)
Patient association	10 (1.9)
None	60 (11.2)

DISCUSSION

Based on the survey results, the specialists who treat CSU throughout Italy are managing a median 40 patients with CSU each year. About half of CSU patients seen by allergy and dermatology specialists have mild CSU whereas the other half have severe disease. However, due to high proportion of specialists of both groups who were not familiar with the UAS and UAS7 scales, the classification of disease severity may not have been sufficiently objective. The limited use of such scales was probably due to the fact that the 2009 EAACI/GA_2LEN/EDF/WAO urticaria guidelines (the current version at the time the survey was conducted) didn't mention them [9]. The importance of this clinical tool has to be stressed both for initial disease severity grading and for monitoring treatment efficacy.

A third of patients are referred to a CSU specialist by a general practitioner, and a fifth by emergency department staff or self-referral at symptom onset. Notably, more dermatologists than allergy specialists established the diagnosis of CSU. This may

simply reflect the fact that, in Italy, dermatology specialists outnumber allergy specialists by three to one, therefore dermatologists are more accessible to patients than allergy specialists. General practitioners were only involved in the diagnosis of 10% of patients with CSU, emphasizing the complexity of diagnosing the disease and the need of referral to a specialist to establish a diagnosis. Overall, diagnosis was established on average 7 months after the appearance of the first symptoms, although time to diagnosis was increased with disease severity, possibly because a more accurate medical history has to be collected from each patient. Highlighting the complexity of the disease itself, 40% of specialists surveyed felt that CSU diagnosis was complex and the difficulty in identifying the cause of the pathology and the multiplicity of tests available for diagnosis were listed as factors contributing to the level of complexity in disease diagnosis. On the other hand the international guidelines strongly recommend only very limited routine diagnostic evaluations in CSU, in order to reduce the number of diagnostic tests.[1]

For most of the allergy and dermatology specialists, the ideal sequence of treatment, at the time of the survey, would be a standard and an increased dose of a non-sedating antihistamine as first-line and second-line treatment, respectively. For third-line treatment for non-responders, specialists tended to favor treatment with an increased dose non-sedating antihistamine in combination with a LTRA and an H_2-antihistamine, or an increased dose non-sedating antihistamine in combination with a steroid or cyclosporine, a regimen especially preferred in more severe disease. Nevertheless, regardless of treatment regimen, over a quarter of all patients with CSU were refractory to the therapy they were receiving, and even complex/aggressive treatment regimens

failed to resolve symptoms in almost half of the patients with severe disease. It should be noted that, at the time of the survey, a new therapeutic option was not yet authorized for CSU treatment. However, since then the approach to patients with refractory CSU has changed: the current EAACI/GA$_2$LEN/EDF/WAO guidelines describe omalizumab as a third-line treatment for urticaria and the Italian regulatory authorities recommend to use omalizumab when patients do not respond to a standard dosage of non-sedating antihistamine.[1]

Moreover, data suggest that continuous therapy is associated to improved outcomes in terms of QoL.[5] However, this is not always reflected in real-life: a survey in patients with CSU in Germany and France showed that 78% of patients were taking medication for their CSU, but only 33% of these were taking it regularly for symptom prevention.[13]

For the specialists surveyed, the main goal of CSU treatment was key symptom resolution (itching and hives) and few considered improving QoL a priority. Importantly, the updated EAACI/GA$_2$LEN/EDF/WAO guidelines strongly recommend complete symptom control, as safely as possible, to be the goal of treatment.[1] In a similar way, the 2009 EAACI/GA$_2$LEN/EDF/WAO guidelines recommended that the aim of treatment was to achieve complete symptom relief [9]. Appropriate management of CSU requires evidence-based guidance; however, only half of the specialists surveyed (more allergy specialists than dermatologists) knew of and used any of the CSU guidelines available, with allergy specialists twice as likely as dermatologists to use guidelines. Notably, the level of knowledge and use of the guidelines correlated with the treatment choices, and therapies selected by physicians not using guidelines

were more likely to be widely different and not in accordance with recommendations.

Similarly, there was a gap in the knowledge of the specialists regarding the main scales used to assess disease activity, with only approximately half of the surveyed specialists acknowledging familiarity with the UAS and UAS7, and only one-sixth acknowledging familiarity with and utilized the CU-QoL questionnaire. The 2014 EAACI/GA$_2$LEN/EDF/WAO guidelines provide a strong recommendation that disease activity should be assessed in clinical care using the UAS7, and that the CU-QoL is one of the validated instruments for assessing QoL impairment and for monitoring disease activity [1]. In the 2009 EAACI/GA$_2$LEN/EDF/WAO guidelines the UAS and UAS7 were not mentioned but the CU-QoL, that had been generated and tested in the Italian language [14] and had only recently been validated in other languages, was recognized as a suitable instrument for the assessment of the health burden both of CSU and its treatment [9].

Among patients surveyed across Italy, the prevalence of CSU has been found to be about the same in women and in men, unlike reports from other countries [3, 15]. Similar to patients with CSU in other countries,[16] about two-thirds of patients reported that CSU had a negative impact on their QoL, affecting both their personal and professional life, and the frequency and level of impact increased with disease severity. More patients with severe disease than those with moderate of mild disease cited stress/anxiety/irritation/insomnia and negative impact on working life as impacting QoL.

In their efforts to obtain symptom relief, over a third of patients had on average consulted two previous physicians. Surprisingly, the number of specialists changed did

not vary significantly when stratified by disease severity. The most common reason for switching providers was dissatisfaction with medical staff. Attending multiple medical centers due to dissatisfaction with treatment and reports of reduced quality of life are in accordance with existing literature in patients with CSU.[4 6-8] A patient survey conducted in Germany and France also reiterated the impact CSU has on QoL and lack of satisfaction with physician care,[16] with patients indicating they were only "somewhat satisfied" with the care they were receiving. Satisfaction with treatment increased if the physician discussed the impact of CSU on emotions with their patient.

There appear to be a mismatch between patients with CSU and specialists as, while two third of the patients reported CSU affecting their QoL, only 8% of specialists considered improving QoL as a priority. Our results suggest that there is a need for specialists to routinely use the CU-QoL, in order to assess how patients are affected by the disease, and the UAS to monitor the disease and provide the most appropriate treatment. It is therefore important for specialists to focus their attention on the burden and the unmet needs of CSU and establishing more satisfying treatment schemes.

Furthermore, most patients did not have patient support services available to them at their medical center.

The limitations of the present study include those inherent in the survey/questionnaire format. Although the questionnaires were designed to minimize bias, there is always a subjective element remaining (e.g. respondents tend to avoid scoring at the end of scales and answer in a way they perceive to be desired by the investigator/be more socially acceptable).[17] A strength of the study is that, by selecting a representative sample of both patients with CSU and of specialists involved in the treatment of CSU in Italy, it

provides a snapshot of the management of this condition from both perspectives, thereby highlighting current gaps in guideline-based care and unmet patient needs.

CONCLUSIONS

In general, patients in Italy with CSU are similar to patients with CSU in other countries. However, there are some gaps in the care of these patients resulting in treatment dissatisfaction and a decreased QoL. These results should be used to improve the treatment of patients with CSU in Italy, in particular by reinforcing the knowledge of the available tools, such as the UAS and CU-QoL questionnaires, which can be used to assist specialists in treating patients with CSU.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Author contributions

MR and NR were responsible for conception and design of the survey. MR was responsible for the acquisition of data; MR and NR had full access to the final data and performed the analysis. MR, NR and OR contributed to data interpretation, to the drafting and critical revision of the manuscript. All authors approved the final version and have final responsibility for content.

Medical writing, editorial, and other assistance

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Competing interests

Oliviero Rossi has been consultant and speaker for Meda, Novartis, MSD, Menarini in the last five years.

Marco Rimoldi is a partner of Stethos Srl and holds shares of this Company. Stethos Srl collaborates with Novartis Farma Italy on several market researches.

Nadia Rota is an employee of Novartis Farma, Italy.

Data sharing statement

No additional data are available.

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Compliance with ethics guidelines

The research was conducted in conformity with the Code of Conduct 2014 of the European Pharmaceutical Market Research association (EphMRA).

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Figure legends

Figure 1. Frequency and regularity of symptoms of chronic spontaneous urticaria in patients with mild disease as reported by their physicians.

Figure 2. (a) Awareness and use of chronic spontaneous urticaria guidelines among the specialists surveyed and (b) guidelines known or followed. All values are percentages.

Figure 3. (a) Therapies received by the 1157 patients with chronic spontaneous urticaria currently treated by 320 specialists surveyed and (b) therapies received by patients with severe and mild forms of the disease.

H2AH, H_2-antihistamine; LTRA, leukotriene receptor antagonist; nsAH, non-sedating antihistamine.

Figure 4. Rates of refractory disease according to current treatment and disease severity.

H2AH, H_2-antihistamine; LTRA, leukotriene receptor antagonist; nsAH, non-sedating antihistamine.

Figure 5. The most frequent reasons for decreased quality of life as reported in the survey of patients with chronic spontaneous urticaria (N=357). Reasons shown are the answers to question 29 of the survey "What aspect of your disease would you indicate as the most impactful on your life?"

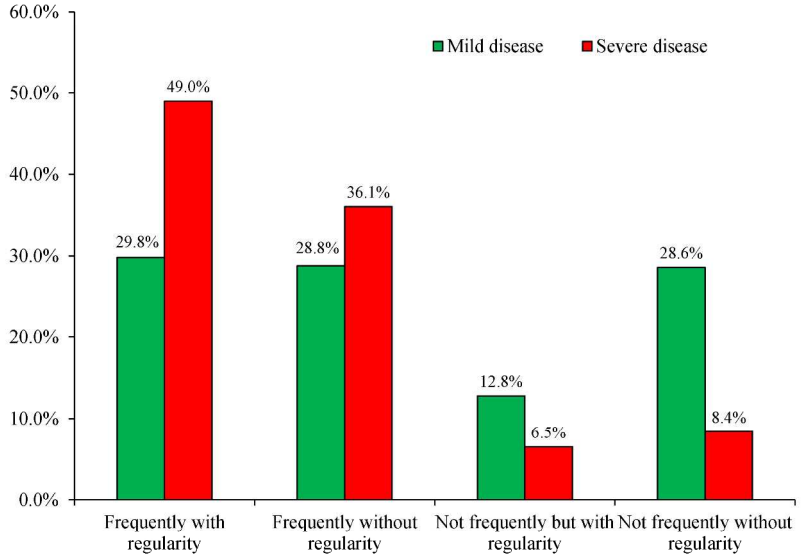

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Figure 1
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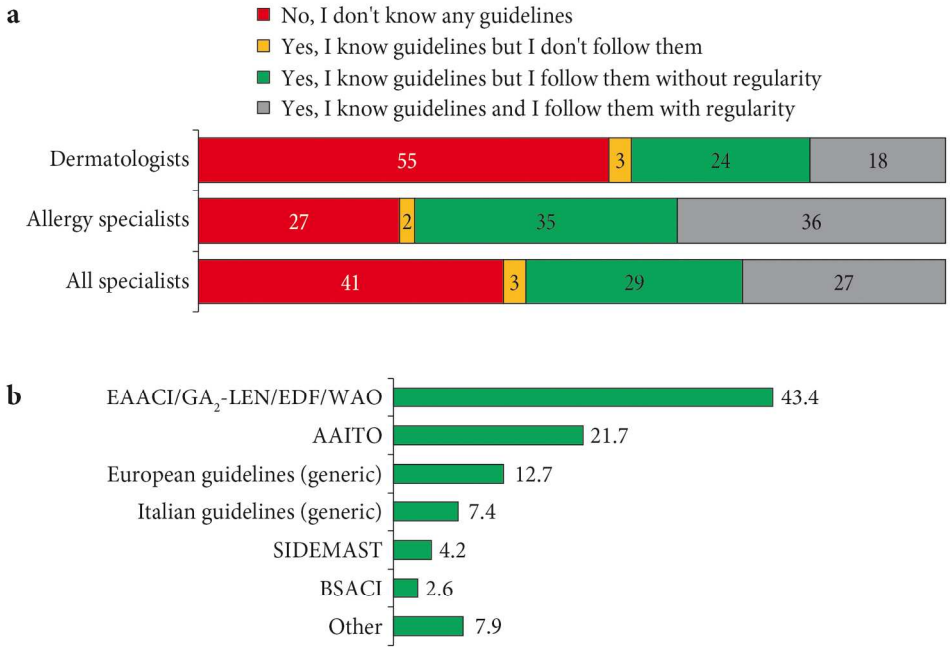

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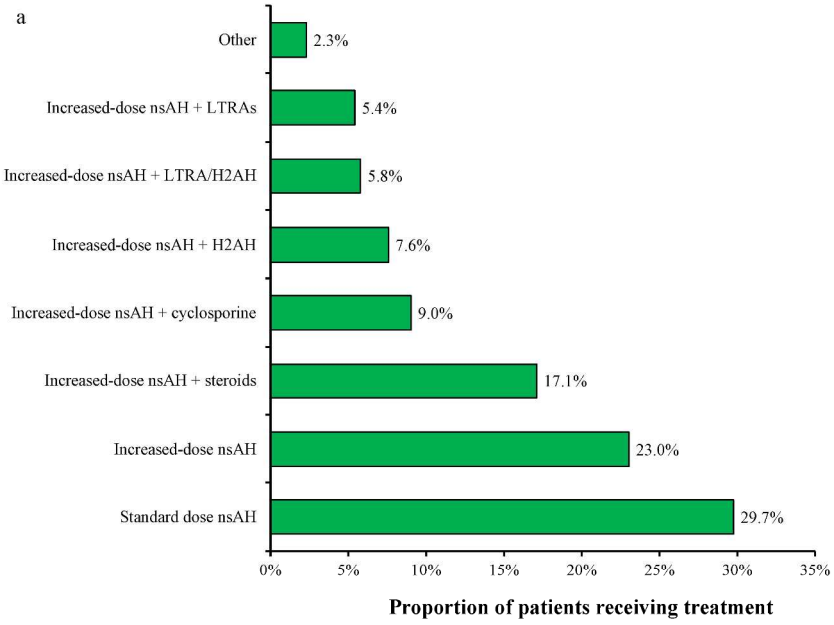

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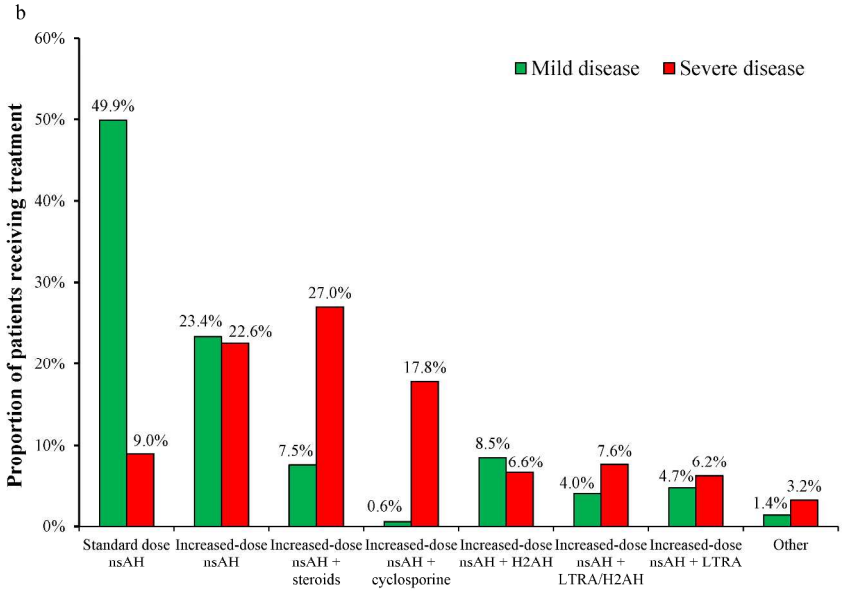

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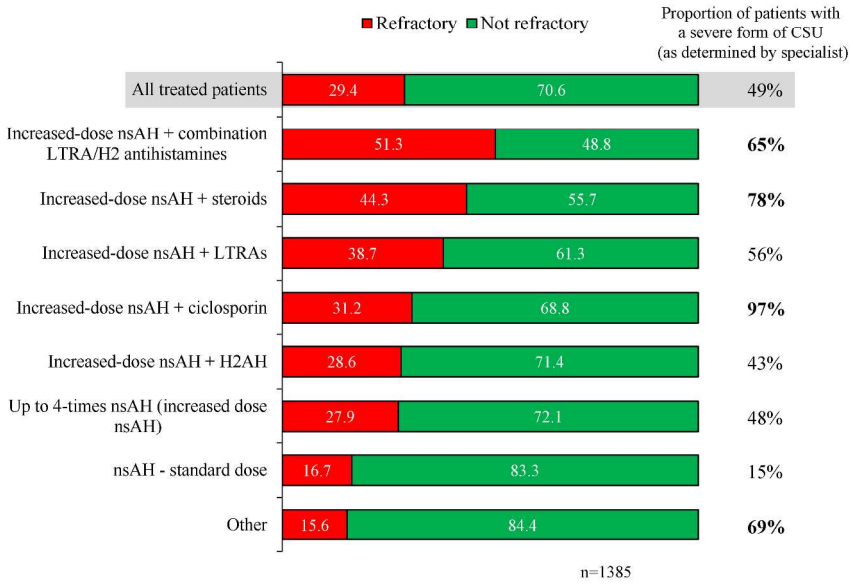

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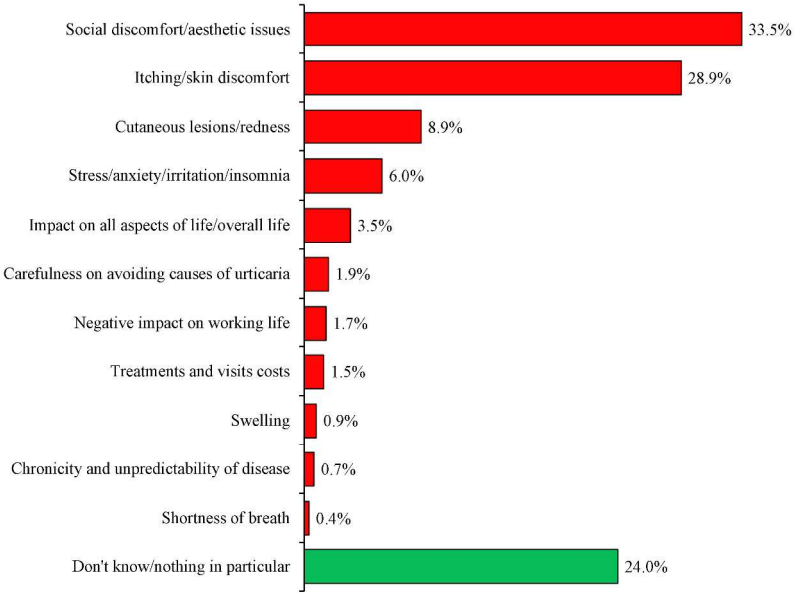

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STETHOS MARKETING RESEARCH

State of the art of CSU in Italy
Quantitative Assessment

DEF – 25/02/14
codice studio Stethos: 131187

INTRODUZIONE

Egregio Dottore, Gentile Dottoressa,
Stethos, istituto di ricerche di mercato specializzato nel campo farmaceutico, sta conducendo uno studio a livello nazionale sulla **Orticaria Spontanea Cronica**, coinvolgendo Medici Specialisti in Dermatologia e Medici Specialisti in Allergologia.
Lo studio non ha alcuna finalità promozionale né commerciale ed è volto ad analizzare ed approfondire come viene gestita oggi questa patologia e quali sono le motivazioni che guidano il clinico nella scelta di trattare farmacologicamente un paziente affetto da CSU. Se accetta di collaborare, le chiediamo cortesemente di compilare il questionario che segue rispondendo ad alcune domande relative alla sua personale esperienza ed opinione nei confronti dei questa patologia. Oltre al questionario, le chiediamo poi di compilare un brevissimo diario relativo agli ultimi 5 pazienti affetti da CSU che lei ha visitato.
L'impegno previsto è di circa 20 minuti.

INFORMATIVA PRIVACY

Desideriamo rassicurarLa circa il fatto che:

- Agiremo nel rispetto di tutte le leggi sulla privacy (D.Lgs. 196/03) per la tutela dei dati personali e delle linee guida emanate da "Market Research Society/European Pharmaceutical Marketing Research Association/ESOMAR".
- Le Sue risposte saranno utilizzate da noi esclusivamente ai fini di una ricerca di mercato.
- Le Sue risposte saranno unite a quelle fornite da altri intervistati e saranno analizzate in forma aggregata e anonima.
- Le Sue risposte saranno gestite con la massima riservatezza e non saranno utilizzate per scopi diversi da quelli indicati né rivelate a terzi senza il Suo consenso.
- Lei ha il diritto di abbandonare l'intervista in qualsiasi momento.

INFORMATIVA FARMACOVIGILANZA

Le garantiamo che qualsiasi informazione fornita verrà trattata in forma strettamente riservata ed anonima. Solamente nel caso in cui dovesse descrivere un evento avverso in un paziente specifico, Le chiederemo cortesemente di consentirci di raccogliere queste informazioni e trasmetterle al nostro cliente (anche se l'evento è già stato da Lei riferito secondo quanto previsto dalla normativa italiana in vigore). In questo caso quindi, chiederemo la sua disponibilità a rinunciare alla riservatezza nel rispetto delle norme espresse nel Codice di Condotta ESOMAR. Qualsiasi altra informazione fornita nel corso dell'intervista sarà considerata assolutamente riservata.

Dom 0 **È disponibile per l'intervista?**

□ SI → proseguire
□ NO → chiudere

PROFILO INTERVISTATO E ANAGRAFICA DEL CENTRO

1. **NOME** _____
2. **COGNOME** _____
3. **OSPEDALE** _____
4. **Indirizzo email** _____
5. **Recapito telefonico** _____

Casistica pazienti CSU

Dom 1. Dottore, Lei si occupa personalmente della diagnosi e del trattamento di pazienti affetti da Orticaria Spontanea Cronica (CSU)?

□ Sì → proseguire con Dom.2
□ No → chiudere, intervista non valida. Non in target.

Dom 2. Quanti sono complessivamente i pazienti affetti da CSU da Lei seguiti nel corso di un anno, compresa l'attività ambulatoriale? |__|__|__|

Dom 3. Di questi pazienti quanti presentano anche un angioedema? |__|__|__|

Dom 4. In media quante nuove diagnosi di CSU effettua in un anno? |__|__|__|

Dom 5. Percentualmente quanti sono tra i Suoi pazienti affetti da CSU quelli che non ricevono alcun trattamento specifico per la CSU?
pazienti non trattati |__|__|__| %

Dom 6. Prendendo in considerazione i soli pazienti CSU trattati come si distribuiscono percentualmente in base al trattamento farmacologico?

solo antistaminico H1 antagonista (dosaggio base)	|__|__|__|%
solo antistaminico H1 antagonista (ad alto dosaggio)	|__|__|__|%
antistaminico H1 in combinazione con antistaminico H2 antagonista e/o antileucotrieni	|__|__|__|%
corticosteroidi (da soli o in associazione ad altre terapie)	|__|__|__|%
inibitori sistemici della calcineurina (ciclosporina)	|__|__|__|%
altri farmaci – diversi da quelli elencati	|__|__|__|%

Dom.7. Conosce l'esistenza di linee guida specifiche per la gestione ed il trattamento dei pazienti affetti da CSU?

1 □ Si le conosco e le adotto con regolarità
2 □ Si le conosco e le adotto anche se non con regolarità
3 □ Sì le conosco ma non le adotto
4 □ No, non le conosco

Se dom.7.=1,2,3
Dom.7.A A quali linee guida fa riferimento? _____ open _____

Dom 7.B Sulla base della sua esperienza clinica, qual è la sequenza di trattamento per un paziente affetto da CSU? Troverà di seguito l'elenco delle diverse tipologie di trattamenti farmacologici, le metta in ordine partendo dal trattamento che abitualmente prescrive per primo.
Graficamente, comparirà la stessa lista indicata a Dom.6 e il medico dovrà indicare per ciascuno l'ordine (1° / 2° / 3 ° …)
1° trattamento
2° trattamento
3° trattamento
4° trattamento
5° trattamento

Dom 7C. Questa sequenza di trattamento, cambia nel caso di paziente CSU affetto anche da angioedema? Se sì, potrebbe indicare come?

□ No rimane la stessa
□ Sì, si modifica in questo modo
1° trattamento
2° trattamento
3° trattamento
4° trattamento
5° trattamento

Dom 8. Per ciascun trattamento, quanti sono indicativamente i pazienti che rimangono sintomatici (non completo controllo della terapia) alla terapia farmacologica?

	% pazienti refrattari
solo antistaminico H1 antagonista (dosaggio base)	|__|__|__|% di pazienti sintomatici
solo antistaminico H1 antagonista (ad alto dosaggio)	|__|__|__|% di pazienti sintomatici
antistaminico H1 in combinazione con antistaminico H2 antagonista e/o antileucotrieni	|__|__|__|% di pazienti sintomatici
corticosteroidi (da soli o in associazione ad altre terapie)	|__|__|__|% di pazienti sintomatici
inibitori sistemici della calcineurina (ciclosporina)	|__|__|__|% di pazienti sintomatici

La gestione del paziente CSU

Dom 9. Mediamente, dopo quanto tempo si arriva alla diagnosi di Orticaria Spontanea Cronica? In altri termini, quanto tempo intercorre tra il momento in cui il paziente si presenta da lei con i sintomi a quando poi viene diagnosticata la forma CSU?
|__|__| mesi |__|__| anni

Dom 10. Troverà di seguito alcune frasi che descrivono i possibili atteggiamenti e comportamenti della classe medica nei confronti della gestione di un paziente con sintomi potenzialmente riconducibili ad una forma di Orticaria Spontanea Cronica. Le chiediamo cortesemente di esprimere una valutazione per ciascuna di esse sulla base di quanto si riconosce nella descrizione. Utilizzi un punteggio da 1 a 10 dove 1 indica "per niente d'accordo / non mi riconosco affatto" e 10 indica "estremamente d'accordo / mi riconosco in pieno".

• a fronte di un paziente potenzialmente affetto da CSU lo invio direttamente all'attenzione di un altro Specialista	**1 2 3 4 5 6 7 8 9 10**
• gestisco in completa autonomia la **terapia farmacologica** (senza rivolgermi ai colleghi per un consulto/un confronto) per i pazienti affetti da CSU	**1 2 3 4 5 6 7 8 9 10**
• prima di arrivare alla **diagnosi** di CSU preferisco aspettare il consulto di un collega (specialista o altro)	**1 2 3 4 5 6 7 8 9 10**

Se a ultimo item della dom.10 valutazione >5 porre Dom.10.A

Dom.10.A

A quale specialista/collega chiede consiglio? _____ open _____

Dom.10.B Qual è il livello di complessità e di difficoltà nell'effettuare una diagnosi di CSU? Utilizzi una scala di valutazione da 1 a 10 dove 1 indica "per nulla complesso" e 10 indica "estremamente complesso". Nel rispondere, consideri i vari steps ed i vari test/esami che è necessario effettuare prima di arrivare alla conferma di una diagnosi di CSU.

1 2 3 4 5 6 7 8 9 10
□ □ □ □ □ □ □ □ □ □

Se Dom.10.B punteggio > 5

Dom.10.C Quali sono i motivi che l'hanno portata a dare questa valutazione? In altri termini, quali elementi considera maggiormente impattanti e onerosi nel percorso di diagnosi?

_____ open _____

Dom.10.D Troverà di seguito le principale scale di misurazione utilizzate a livello mondiale per valutare e definire il livello di gravità della CSU. Per ognuna dovrebbe indicare se la conosce e la utilizza.

• **UAS** (urticaria activity score)	□ non la conosco □ la conosco ma non la utilizzo □ la utilizzo
• **UAS 7** (urticaria activity score 7 days)	□ non la conosco □ la conosco ma non la utilizzo □ la utilizzo
• **CU-QoL** (chronic urticaria quality of life)	□ non la conosco □ la conosco ma non la utilizzo □ la utilizzo

Dom.10.E Vi sono degli elementi /degli strumenti / delle necessità ad oggi non soddisfatte che potrebbero eventualmente agevolarla nella fase di diagnosi della patologia?

_____ open _____

Driver di scelta di una terapia

Dom 11. Pensi ora al momento in cui deve decidere quale terapia iniziare in un paziente affetto da CSU. Quali sono i principali obiettivi terapeutici che si pone di raggiungere per un paziente CSU? Indichi per cortesia almeno i primi 2 obiettivi terapeutici mettendoli in ordine di importanza.

1° obiettivo terapeutico |_____|
2° obiettivo terapeutico |_____|
Altri obiettivi terapeutici |_____|

Dom 12. E più nello specifico, quali sono gli elementi che prende in considerazione nella scelta della terapia?

Troverà di seguito una serie di caratteristiche di un farmaco, per ognuno di essi dovrebbe indicare quanto lo ritiene importante attribuendogli un punteggio da 1 a 10, dove 1 indica "per niente importante" e 10 indica "decisamente importante".

caratteristiche	punteggio
La rapidità d'azione	__ /10
La durata d'azione	__ /10
L'efficacia del trattamento	__ /10
La via di somministrazione	__ /10
La frequenza di somministrazione	__ /10
Il profilo di sicurezza	__ /10
L'impatto della terapia sulla qualità di vita del paziente	__ /10
Il costo della terapia	__ /10
Il monitoraggio del paziente necessario dopo l'inizio della terapia	__ /10

Se Dom.12 item "impatto terapia su qualità di vita del paziente" valutazione ≥ 6

Dom 12.A Quali sono gli aspetti/gli elementi della malattia che il paziente considera più critici, di difficile gestione e di maggior impatto sulla sua vita? Indichi per cortesia i primi 3 aspetti mettendoli in ordine di importanza.

1° 2° 3°

- prurito
- angioedema
- imprevedibilità dei sintomi
- impatto della malattia sull'aspetto fisico
- depressione
- ponfi-pomfi
- impatto della malattia sulle relazioni sociali
- mal di testa

Dom 13.Ora dovrebbe assegnare un punteggio ai principali trattamenti farmacologici a disposizione dei clinici per il trattamento della CSU, per ognuna delle caratteristiche che ha appena valutato. Può assegnare un punteggio da 1 a 10, dove 1 indica una valutazione "decisamente negativa" e 10 indica, invece, una valutazione "decisamente positiva" della caratteristica rispetto al farmaco.

Caratteristica	ANTISTAMINICI	CICLOSPORINA	ANTISTAMINICI + CORTISONICI	ANTISTAMINICI +ANTILEUCOTRIENI
La rapidità d'azione	__ /10	__ /10	__ /10	__ /10
La durata d'azione	__ /10	__ /10	__ /10	__ /10
L'efficacia del trattamento	__ /10	__ /10	__ /10	__ /10
La via di somministrazione	__ /10	__ /10	__ /10	__ /10
La frequenza di somministrazione	__ /10	__ /10	__ /10	__ /10
Il profilo di sicurezza	__ /10	__ /10	__ /10	__ /10
L'impatto della terapia sulla qualità di vita del paziente	__ /10	__ /10	__ /10	__ /10
Il costo della terapia	__ /10	__ /10	__ /10	__ /10
Il monitoraggio del paziente necessario dopo l'inizio della terapia	__ /10	__ /10	__ /10	__ /10

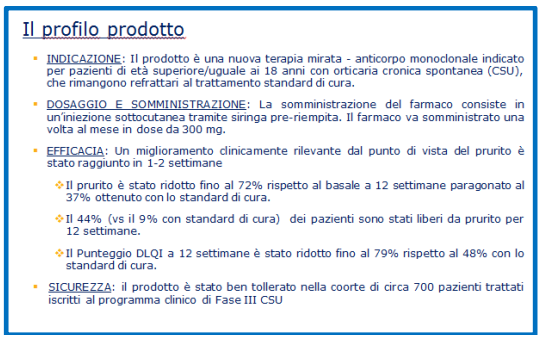
Dom 14.Più in generale, nella scelta di iniziare una terapia, quanto incide la richiesta da parte del paziente? Nel rispondere, utilizzi un punteggio da 1 a 6, dove il punteggio 1 indica che "non è in alcun modo influente quanto chiede il paziente**" e 6 indica che, invece**, "è decisamente influente la richiesta da parte del paziente".

Richiesta del paziente __ / 6

Dom 15. Sempre parlando di CSU, è a conoscenza di farmaci attualmente in sperimentazione o prossimi al lancio con l'indicazione per questa patologia? Se sì, quali sono questi farmaci che lei conosce? Indicare il brand e/o il nome dell'Azienda.

□ Sì → **quali** _____
□ No

Troverà di seguito un profilo prodotto


Il profilo prodotto

- INDICAZIONE: Il prodotto è una nuova terapia mirata - anticorpo monoclonale indicato per pazienti di età superiore/uguale ai 18 anni con orticaria cronica spontanea (CSU), che rimangono refrattari al trattamento standard di cura.
- DOSAGGIO E SOMMINISTRAZIONE: La somministrazione del farmaco consiste in un'iniezione sottocutanea tramite siringa pre-riempita. Il farmaco va somministrato una volta al mese in dose da 300 mg.
- EFFICACIA: Un miglioramento clinicamente rilevante dal punto di vista del prurito è stato raggiunto in 1-2 settimane
  - Il prurito è stato ridotto fino al 72% rispetto al basale a 12 settimane paragonato al 37% ottenuto con lo standard di cura.
  - Il 44% (vs il 9% con standard di cura) dei pazienti sono stati liberi da prurito per 12 settimane.
  - Il Punteggio DLQI a 12 settimane è stato ridotto fino al 79% rispetto al 48% con lo standard di cura.
- SICUREZZA: il prodotto è stato ben tollerato nella coorte di circa 700 pazienti trattati iscritti al programma clinico di Fase III CSU

Dom 16.Sa di quale farmaco stiamo parlando?

☐Sì |_____open _____| → proseguire con Dom.17
☐No → passare a Dom.18

Se dom.16=si

Dom 17. Attraverso quali fonti di informazione ne è venuto a conoscenza? Sono possibili più risposte

□ informatori / area medica dell'Azienda
□ convegni /congressi
□ pubblicazioni su riviste specializzate
□ internet
□ studi clinici
□ Altro _____open _____

Dom 18. Basandosi sulle sue conoscenze attuali/sulla descrizione che le abbiamo mostrato qual è la sua opinione nei confronti di questo farmaco per il trattamento della CSU?

□ Estremamente positiva
□ Positiva
□ Abbastanza positiva
□ Né positiva né negativa
□ Abbastanza negativa
□ Negativa
□ Estremamente negativa

Dom 19. Quali sono i principali punti di forza di questo farmaco? |_____ open _____|

Dom 20. E quali i punti di debolezza? |_____ open _____|

Dom 21. Sulla base delle sue conoscenze / sulla base del profilo prodotto appena descritto, quale potrebbe essere il profilo paziente CSU "tipo per questo farmaco"?
|_____ open _____|

Dom 22. Con l'arrivo di questo nuovo farmaco per il trattamento della CSU, quale sarebbe dal suo punto di vista la sequenza ideale di trattamento? In altri termini, rispetto a quanto ci ha indicato prima dove si posizionerebbe questo farmaco?

- solo antistaminico H1 antagonista (dosaggio base)
- solo antistaminico H1 antagonista (ad alto dosaggio)
- antistaminico H1 in combinazione con antistaminico H2 antagonista e/o antileucotrieni
- corticosteroidi (da soli o in associazione ad altre terapie)
- inibitori sistemici della calcineurina (ciclosporina)
- nuovo farmaco appena descritto
- altro farmaco diverso da quelli elencati

Dom 23. Questa sequenza di trattamento, cambierebbe nel caso di paziente CSU affetto anche da angioedema? Se sì, potrebbe indicare come?

☐ No rimane la stessa
☐ Si, si modifica in questo modo
1° trattamento
2° trattamento
3° trattamento
4° trattamento

5° trattamento

Dom 24. Cosa la invoglierebbe ad utilizzare questo farmaco come 2° linea di trattamento? Quali elementi prenderebbe in considerazione per un suo utilizzo in 2° linea?
_____ open _____

Dom 25. Considerando tutti i suoi pazienti affetti da CSU, quanti di questi potrebbero essere eleggibili al trattamento con il farmaco?
|__|__|__|

Dom 26. Siamo giunti al termine del questionario. Pensi ora a tutti i trattamenti che ha Immagini ora che il farmaco sia già disponibile sul mercato. Sulla base delle sue attuali conoscenze ed informazioni, quanto sarebbe propenso a prescrivere questo farmaco? Per rispondere utilizzi una scala di valutazione da 1 a 10 dove 1 indica "non lo prescriverei in alcun modo" e 10 indica "assolutamente lo prescriverei".

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Dom 27.Siamo giunti al termine del questionario. Sulla base della sua esperienza e pratica clinica, quali sono ad oggi i bisogni e le necessità che ancora non trovano una risposta con le terapie attualmente disponibili? Troverà di seguito una serie di elementi, per ognuno dovrebbe assegnare un punteggio per indicare quanto tale bisogno risulta ad oggi non soddisfatto dai trattamenti disponibili. Utilizzi una scala da 1 a 10 dove 1 indica che "non è in alcun modo un elemento critico/il bisogno è soddisfatto" e 10 indica "elemento assolutamente critico/bisogno decisamente non soddisfatto".

Item 9 compare se a dom.10.D UAS ≠ non lo conosco
Item 10 compare se a dom.10.D UAS 7 days ≠ non lo conosco

	caratteristiche	punteggio
1	La possibilità di tenere completamente sotto controllo la malattia	__ /10
2	La possibilità di controllare i sintomi della malattia	__ /10
3	Miglioramento QoL del paziente – da un punto di vista pratico/delle attività fisiche	__ /10
4	Miglioramento QoL del paziente – da un punto di vista psicologico	__ /10
5	Farmaci approvati specificatamente per la CSU	__ /10
6	Farmaci a minor frequenza di somministrazione	__ /10
7	Farmaci caratterizzati da un livello di sicurezza e di tollerabilità accettabili	__ /10
8	Farmaci ad azione rapida	__ /10
9	Miglioramento del paziente su scala UAS (urticaria activity scale)	__ /10
10	Miglioramento del paziente su scala UAS 7 (urticaria activity scale 7 days)	__ /10

Dom 28. Prima di passare alla compilazione dei diari pazienti, come ultimo sforzo le chiediamo di indicarci, se vuole, quelli che sono i Medici Specialisti (in Dermatologia o Allergologia) che Lei considera punti di riferimento in <u>Italia</u> per il trattamento della CSU.

1° nome |_____| cognome |_____| ospedale |_____| città|_____|
2° nome |_____| cognome |_____| ospedale |_____| città|_____|
3° nome |_____| cognome |_____| ospedale |_____| città|_____|

La compilazione del questionario è ultimata. Le chiediamo ora di accedere alla seconda sezione per compilare un brevissimo diario per gli ultimi 5 pazienti affetti da CSU che ha visitato.

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Quantitative Assessment

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INTRODUCTION

Dear Doctor,
Stethos, a market research company specialising in the pharmaceutical sector, is conducting a nation-wide survey among Physician Specialists in Dermatology and Physician Specialists in Allergology on the subject of **Chronic Spontaneous Urticaria**,
The survey has no promotional or commercial purposes and aims to analyse in depth how this disease is managed and what motivations guide clinicians in their decision to commence a pharmacological therapy in affected patients. If you agree to take part, we would kindly ask you to complete the following questionnaire by answering some questions concerning your personal experience and your opinions about this disease. In addition to the questionnaire, we also ask you to complete a very short patient diary for each of the last 5 CSU patients you have assessed.
The expected time commitment is approximately 20 minutes.

PRIVACY STATEMENT
Please be assured that:

- Our actions will comply with all the laws on privacy (Italian Law no. 196/03) for the protection of personal data and the guidelines issued by the "Market Research Society/European Pharmaceutical Marketing Research Association/ESOMAR".
- Your answers will be used exclusively for the purposes of market research.
- Your answers will be combined with those of other respondents and will be analysed in anonymous and pooled form.
- Your answers will be handled with maximum confidentiality and will not be used for any purpose other than those indicated, nor will they be disclosed to any third party without your consent.
- You have the right to terminate the interview at any time.

PHARMACOVIGILANCE-RELATED INFORMATION
We guarantee that any information supplied will be handled with maximum confidentiality and anonymity. Only in the case that you should describe an adverse event in a specific patient, we will ask you for permission to collect this information and forward it to our client (even if you have already reported the event in accordance with the Italian regulations in force). Therefore, in this case, you will be asked to waive your right to confidentiality in compliance with the rules expressed in the ESOMAR Code of Conduct. Any other information provided in the course of the interview shall be considered absolutely confidential.

Q. 0 **Are you willing to take part in the interview?**
□ YES → continue
□ NO → close

RESPONDENT'S PROFILE AND DETAILS OF CENTRE

1. **NAME** _____
2. **SURNAME** _____
3. **HOSPITAL** _____
4. **Email address** _____
5. **Telephone number** _____

CSU caseload

Q. 1. Do you personally conduct the diagnosis and treatment of patients affected by Chronic Spontaneous Urticaria (CSU)?
□ Yes → go on to Q.2
□ No → close, interview not valid. Not in target population.

Q. 2. Overall, how many CSU patients do you care for in a year, including during your ambulatory activity? |__|__|__|

Q. 3. How many of these patients are also affected by angioedema? |__|__|__|

Q. 4. On average, how many new cases of CSU do you diagnose in a year? |__|__|__|

Q. 5. What percentage of your CSU patients receive no specific treatment for CSU?
untreated patients |__|__|__| %

Q. 6. Taking into consideration your treated CSU patients only, how are they distributed with regard to their pharmacological treatment?

only H1-antihistamine (standard dose)	|__|__|__|%
only H1-antihistamine (increased-dose)	|__|__|__|%
H1-antihistamine in combination with leukotriene antagonist/H2-antihistamine	|__|__|__|%
steroids (alone or in combination with other drugs)	|__|__|__|%
systemic calcineurin inhibitors (cyclosporin)	|__|__|__|%
other drugs than those listed	|__|__|__|%

Q. 7. Are you aware of the existence of specific guidelines on the management and treatment of patients affected by CSU?

1 □ Yes, I know the guidelines and I apply them regularly
2 □ Yes, I know the guidelines and I apply them, though not regularly
3 □ Yes, I know the guidelines but I don't apply them
4 □ No, I don't know the guidelines

If Q.7.=1,2,3
Q.7.A Which guidelines are you referring to? _____ open _____

Q.7.B Based on your clinical experience, what is the treatment sequence for a patient affected by CSU? Below you will find a list of the different types of pharmacological treatments: please order them starting from the treatment you normally prescribe first.
Graphically, the same list shown in Q. 6 will appear and the doctor will have to indicate the order for each item on the list (1 / 2 / 3 …)
Treatment 1
Treatment 2
Treatment 3
Treatment 4
Treatment 5

Q.7C. Does this treatment sequence change in the case of a CSU patient also affected by angioedema? If so, could you indicate how it changes?

□ No it remains unchanged
□ Yes, the sequence is changed as follows Treatment 1
Treatment 2
Treatment 3
Treatment 4
Treatment 5

Q. 8. For each treatment, approximately how many patients remain symptomatic during the pharmacological treatment (incomplete control)?

	% refractory patients
only H1-antihistamine (standard dose)	|__|__|__|% symptomatic patients
only H1-antihistamine (increased-dose)	|__|__|__|% symptomatic patients
H1-antihistamine in combination with leukotriene antagonist/ H2-antihistamine	|__|__|__|% symptomatic patients
steroids (alone or in combination with other drugs)	|__|__|__|% symptomatic patients
systemic calcineurin inhibitors (cyclosporin)	|__|__|__|% symptomatic patients

Management of the CSU patient

Q. 9. On average, how long does it take to arrive at a diagnosis of Chronic Spontaneous Urticaria? In other words, how much time elapses between when the patient presents to you with the symptoms and when CSU is diagnosed?
|__|__| months |__|__| years

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Q. 10. Below you will find some statements describing physicians' possible attitudes and approaches to the management of a patient presenting with symptoms potentially related to Chronic Spontaneous Urticaria. Please rate them based on the extent to which you identify with each statement. Give a score from 1 to 10 where 1 indicates "strongly disagree / not true for me at all" and 10 indicates "strongly agree / very true for me".

• If a patients has the symptoms of CSU **I directly send him to other colleague** •	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
• **I autonomously manage the therapy** to a CSU patient • (without seeking a consultation/discussion with colleagues)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
• To diagnosis CSU **I usually prefer to consult with a colleague**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

If the last item of Q.10 was rated >5 proceed with Q.10.A

Q.10.A
Which specialist/colleague do you seek advice from? _____ open _____

Q.10.B What is the level of complexity and difficulty in formulating a diagnosis of CSU? Give a rating from 1 to 10 where 1 indicates "not at all complex" and 10 indicates "extremely complex". In answering, consider the various steps and tests/investigations that are required before a diagnosis of CSU can be confirmed.

1 2 3 4 5 6 7 8 9 10
□ □ □ □ □ □ □ □ □ □

If Q.10.B was rated >5

Q.10.C What reasons led you to give this rating? In other words, what elements do you consider to be most impacting and burdensome in the diagnostic process?
_____ open _____

Q.10.D Below you will find the major severity scales used worldwide to rate and determine the level of CSU severity. For each scale, please indicate whether you are familiar with it and whether you use it in your practice.

• **UAS** (urticaria activity score)	□ I'm not familiar with it □ I'm familiar with it but I don't use it □ I use it
• **UAS 7** (urticaria activity score 7 days)	□ I'm not familiar with it □ I'm familiar with it but I don't use it □ I use it
• **CU-QoL** (chronic urticaria - quality of life)	□ I'm not familiar with it □ I'm familiar with it but I don't use it □ I use it

Q. 10.E Are there any elements /instruments /unmet needs that could possibly facilitate you in diagnosing the disease?
_____ open _____

Treatment-decision drivers

Q. 11. Think about when you decide what treatment to initiate in a patient affected by CSU. What are the main treatment goals that you hope to achieve for a CSU patient? Please indicate at least the first 2 treatment goals by placing them in order of importance.
1st treatment goal |_____|
2nd treatment goal |_____|
Other treatment goals |_____|

Q. 12. And, more in detail, what elements do you take into account when deciding on a treatment?
Below you will find several characteristics of a pharmacological treatment. For each characteristic, please indicate how important you believe it to be by rating it from 1 to 10, where 1 indicates "not at all important" and 10 indicates "definitely important".

characteristics	rating

Rapidity of drug action	__ /10
Duration of drug action	__ /10
Efficacy of treatment	__ /10
Way of administration	__ /10
Frequency of administration	__ /10
Drug safety	__ /10
Impact of the treatment on the patient's quality of life	__ /10
Cost of the treatment	__ /10
Patient monitoring required after beginning the treatment	__ /10

If Q.12 "impact of the treatment on the patient's quality of life" was rated ≥6

Q.12.A What aspects/elements does the patient consider to be most critical, difficult to cope with and having the greatest impact on his/her life? Please indicate the first 3 aspects in order of importance.

1st **2nd** **3rd**

- itching
- angioedema
- unpredictability of symptoms
- impact of disease on physical appearance
- depression
- hives
- impact of the disease on social relations
- headache

Q. 13. Now please rate the main pharmacological therapies available to clinicians for the treatment of CSU, from the point of view of the characteristics rated in Q.12. Rate them from 1 to 10, where 1 indicates a "definitely negative" rating and 10 indicates a "definitely positive" rating of the therapy in relation to the characteristic.

Characteristic	ANTIHISTAMINES	CYCLOSPORIN	ANTIHISTAMINES + STEROIDS	ANTIHIISTAMINES +LEUKOTRIENE ANTAGONISTS
Rapidity of action drug	__ /10	__ /10	__ /10	__ /10
Duration of action drug	__ /10	__ /10	__ /10	__ /10
Efficacy of treatment	__ /10	__ /10	__ /10	__ /10
Way of administration	__ /10	__ /10	__ /10	__ /10
Frequency of administration	__ /10	__ /10	__ /10	__ /10
Drug Safety	__ /10	__ /10	__ /10	__ /10
Impact of the treatment on the patient's quality of life	__ /10	__ /10	__ /10	__ /10
Cost of the treatment	__ /10	__ /10	__ /10	__ /10
Patient monitoring required after beginning the treatment	__ /10	__ /10	__ /10	__ /10

Q. 14. More in general, how much does a patient's request for treatment affect your decision to start a therapy? When answering, give a rating from 1 to 6, where 1 indicates that "the patient's request has no influence" **and 6 indicates that** "the patient's request has a strong influence".

Patient's request __ / 6

Q. 15. Still on the subject of CSU, do you know of any pharmaceutical products currently being tested or about to be launched that are indicated for this disease? If so, what pharmaceuticals do you know of? Indicate the brand and/or the company.

□ YES → **which** _____

□ NO

Below is a product profile

Product profile

- INDICATION: the product is a new targeted monoclonal antibody therapy indicated for patients aged 18 years or older with chronic spontaneous urticaria (CSU) who remain unresponsive to standard care
- DOSAGE AND ADMINISTRATION: Administration of the product is by subcutaneous injection via pre-filled syringe. The drug is administered once monthly at a dose of 300 mg.
- EFFICACY: A clinically relevant improvement of itching was achieved in 1-2 weeks
  - Itching decreased to 72% at 12 weeks compared with baseline versus 37% with standard care
  - 44% of patients (vs 9% with standard care) remained free of itching for 12 weeks
  - DLQI score at 12 weeks decreased to 79% compared to 48% with standard care
- SAFETY: the product was well tolerated in the cohort of approximately 700 treated patients enrolled in the Phase III CSU trial

Q. 16. Do you know which pharmaceutical product the profile refers to?

□ Yes |_____open _____| → go to Q.17
□ No → proceed to Q.18

If Q.16=yes

Q. 17. Through what sources of information did you learn about the product? More than one answer is possible

□ pharmaceutical sales representatives / company's medical department
□ meetings /conferences
□ journal publications
□ internet
□ clinical trials
□ other _____open _____

Q. 18. Based on your current knowledge / on the description supplied to you, how do you rate your opinion about this medicinal product for the treatment of CSU?

□ Extremely positive
□ Positive
□ Somewhat positive
□ Neither positive nor negative
□ Somewhat negative
□ Negative
□ Extremely negative

Q. 19. What are the main strengths of this product? |_____ open _____|

Q. 20. And its weaknesses? |_____ open _____|

Q. 21. Based on your knowledge / on the product profile provided, what could be a typical CSU patient profile for this pharmaceutical product?

|_____ open _____|

Q. 22. With the advent of this new pharmaceutical product for the treatment of CSU, what do you think would be the ideal treatment sequence? In other words, relative to the sequence you indicated previously what would be the position of the new product?

- only H1-antihistamine (standard dose)
- only H1-antihistamine (increased-dose)
- H1-antihistamine in combination with leukotriene antagonist/H2-antihistamine
- steroids (alone or combined with other drug)
- systemic calcineurin inhibitors (cyclosporin)
- new pharmaceutical product
- other pharmaceutical product than those listed

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Q. 23. Would this treatment sequence change in the case of a CSU patient also affected by angioedema? If yes, could you indicate how?

- ☐ No, it would remain unchanged
- ☐ Yes, it would change as follows Treatment 1
  Treatment 2
  Treatment 3
  Treatment 4
  Treatment 5

Q. 24. What would induce you to use this product as a second-line treatment? What elements would you take into account for its use as a second-line treatment?

_____ open _____

Q. 25. Considering all of your CSU patients, how many of them might be eligible for treatment with the new product?

|__|__|__|

Q. 26. We have reached the end of the questionnaire. Think of all the treatments available and imagine that the new product is already on the market. Based on your current knowledge and information, rate your willingness to prescribe this medicinal product. To answer, use a scale from 1 to 10 where 1 indicates "I would definitely not prescribe it" and 10 indicates "I would definitely prescribe it".

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Q. 27. We have reached the end of the questionnaire. Based on your experience and clinical practice, what are the needs and requirements that remain unmet by the currently available treatments? Below you will find a series of elements. For each, please rate the extent to which the need has not been met by the available treatments. Use a scale from 1 to 10 where 1 indicates "this is not a critical element/this need has been met" and 10 indicates "absolutely critical element/this need has definitely not been met".

Item 9 appears if Q.10.D UAS ≠ I'm not familiar with it
Item 10 appears if Q.10.D UAS 7 days ≠ I'm not familiar with it

	characteristics	rating
1	The possibility to achieve complete control of the disease	__ /10
2	The possibility to control the symptoms of the disease	__ /10
3	Improvement of patient's QoL – in terms of practical aspects/physical activity	__ /10
4	Improvement of patient's QoL – in terms of psychological aspects	__ /10
5	Drugs specifically approved for CSU	__ /10
6	Drugs with a low frequency of administration	__ /10
7	Drugs with acceptable safety and tolerability levels	__ /10
8	Fast-acting drugs	__ /10
9	Improvement of patient on UAS (urticaria activity scale)	__ /10
10	Improvement of patient on UAS 7 (urticaria activity scale 7 days)	__ /10

Q. 28. Before proceeding with the patient diaries, as a very last effort, we would like you to indicate, if you wish, the details of the Specialist Physicians (in Dermatology or Allergology) that you consider to be reference physicians in Italy for the treatment of CSU.

1 name |_____| surname |_____| hospital |_____| city|_____|
2 name |_____| surname |_____| hospital |_____| city|_____|
3 name |_____| surname |_____| hospital |_____| city|_____|

The questionnaire is complete. Please access section two to compile a very short diary for the last 5 CSU patients you have assessed.

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Scheda Paziente

CSU Physicians Insights quantitative assessment

DEF 25/02/2014
codice studio Stethos: 131187

Compilare le schede relative agli ultimi **5 pazienti affetti da CSU che ha visitato e che sono in trattamento per la patologia** (a prescindere dal tipo di terapia).La preghiamo di prendere in considerazione i soli pazienti CSU trattati e di non considerare i pazienti che non seguono, oggi, alcuna terapia farmacologica.

IL PAZIENTE

1. Sesso: ☐M ☐F **2. Età**: |__|__| **3. Anno comparsa dei primi sintomi:** |__|__|__|__|

LA DIAGNOSI

4. Il paziente si è rivolto a Lei subito alla comparsa dei primi sintomi oppure dopo essere andato da altri medici o al pronto soccorso?

- ☐ subito alla comparsa dei primi sintomi
- ☐ dopo essere andato al pronto soccorso
- ☐dopo essere andato dal MMG
- ☐ dopo essersi rivolto ad altro Specialista → specificare quale Specialista _____
- ☐ non sa / non ricorda

5. Quali esami/test ha prescritto al paziente quando la prima volta si è presentato da lei con i sintomi? ☐ test1 ☐test2 ☐ test3 ☐ test4 ☐ test5 ☐ test 6 ….

6. Ricorda quali sono stati i sintomi che il paziente presentava? ☐ No ☐ Si_____-

7. La diagnosi di CSU a questo paziente è stata effettuata da Lei o da altro medico? ☐ da lei ☐ da MMG ☐ altro Dermatologo ☐ altro Allergologo ☐ al pronto soccorso ☐ altro Specialista → altro Specialista _____ specificare _____

8. Dopo quanto tempo, dalla comparsa dei primi sintomi, si è arrivati alla diagnosi di CSU? |__|__| mesi / |__|__| anni

9. In questo paziente i sintomi della CSU si ripresentano con una certa frequenza e regolarità oppure no?

- ☐ Si presentano frequentemente con una certa regolarità
- ☐ Si presentano frequentemente ma senza regolarità
- ☐ Non si presentano frequentemente ma hanno una certa regolarità
- ☐ Non si presentano frequentemente né hanno regolarità

9.A Ogni quanto si ripresentano i sintomi? _____open _____

ATTUALE TERAPIA

10. Attuale terapia:

- ☐ solo antistaminico H1 antagonista (dosaggio base)
- ☐ solo antistaminico H1 antagonista (ad alto dosaggio)
- ☐ antistaminico H1 in combinazione con antistaminico H2 antagonista
- ☐ antistaminico H1 antagonista in combinazione con antileucotrieni
- ☐ antistaminico H1 in combinazione con antistaminico H2 antagonista e antileucotrieni
- ☐ corticosteroidi (da soli o in associazione ad altre terapie)
- ☐ inibitori sistemici della calcineurina (ciclosporina)
- ☐ altro farmaco / altra associazione di farmaci

11. Data inizio trattamento attuale |__|__|__|__| / |__|__|

12.A La terapia seguita dal paziente è … ☐ una terapia cronica ☐ una terapia al bisogno (che il paziente assume alla ricomparsa dei sintomi)

12.B Il paziente è refrattario all'attuale terapia farmacologica? Ossia, il paziente continua ad essere sintomatico nonostante l'assunzione della terapia? ☐ Sì ☐ No

13. In passato il paziente ha seguito altre terapie per la CSU?

- ☐ No, nessun'altra terapia in passato (né topiche né sistemiche)
- ☐ Sì, ma in passato solo terapie topiche
- ☐ Sì, in passato altre terapie sistemiche (orali o iniettive)

Se altre terapie farmacologiche orali o iniettive in passato

14. Quali altre terapie aveva seguito il paziente? Le indichi in base alla sequenza con cui sono state prescritte, riportando anche i motivi per cui si è deciso di interromperla.

	Indicare terapia	**Indicare motivo per cui si è deciso di interromperla**
1° terapia	☐ solo antistaminico H1 antagonista (dosaggio base) ☐ solo antistaminico H1 antagonista (ad alto dosaggio) ☐ antistaminico H1 in combinazione con antistaminico H2 antagonista ☐ antistaminico H1 antagonista in combinazione con antileucotrieni ☐ antistaminico H1 in combinazione con antistaminico H2 antagonista e antileucotrieni ☐ corticosteroidi (da soli o in associazione ad altre terapie) ☐ inibitori sistemici della calcineurina (ciclosporina) ☐ altro farmaco / altra associazione di farmaci	☐ tollerabilità ☐ efficacia non adeguata ☐ richiesta del paziente ☐ scarsa compliance ☐ per migliorare la QoL del paziente ☐ altro motivo_____
2° terapia	**Indicare terapia** ☐ solo antistaminico H1 antagonista (dosaggio base) ☐ solo antistaminico H1 antagonista (ad alto dosaggio) ☐ antistaminico H1 in combinazione con antistaminico H2 antagonista	**Indicare motivo per cui si è deciso di interromperla** ☐ tollerabilità ☐ efficacia non adeguata ☐ richiesta del paziente

	☐ antistaminico H1 antagonista in combinazione con antileucotrieni	☐ scarsa compliance ☐ per migliorare la QoL del paziente ☐ altro motivo_____
	☐ antistaminico H1 in combinazione con antistaminico H2 antagonista e antileucotrieni	
	☐ corticosteroidi (da soli o in associazione ad altre terapie)	
	☐ inibitori sistemici della calcineurina (ciclosporina)	
	☐ altro farmaco / altra associazione di farmaci	
3° terapia	**Indicare terapia**	**Indicare motivo per cui si è deciso di interromperla**
	☐ solo antistaminico H1 antagonista (dosaggio base)	☐ tollerabilità ☐ efficacia inadeguata ☐ richiesta del paziente ☐ scarsa compliance ☐ per migliorare la QoL del paziente ☐ altro motivo_____
	☐ solo antistaminico H1 antagonista (ad alto dosaggio)	
	☐ antistaminico H1 in combinazione con antistaminico H2 antagonista	
	☐ antistaminico H1 antagonista in combinazione con antileucotrieni	
	☐ antistaminico H1 in combinazione con antistaminico H2 antagonista e antileucotrieni	
	☐ corticosteroidi (da soli o in associazione ad altre terapie)	
	☐ inibitori sistemici della calcineurina (ciclosporina)	
	☐ altro farmaco / altra associazione di farmaci	

Se paziente trattato attualmente & prima terapia seguita dal paziente (dom. 13= NO oppure SI ma in passato solo topiche)

15. Per quale motivo ha deciso di iniziare proprio questa terapia con "attivare item indicati a domanda 10"? _____

Se paziente trattato attualmente & altre terapie farmacologiche in passate (dom. 13=in passato altre terapie f.co orale o iniettive)

16. Per quale motivo ha poi deciso di iniziare proprio questa terapia con "attivare item indicati a domanda 10"? _____

A TUTTI

17. Ogni quanto tempo visita questo paziente? ☐ ogni mese ☐ ogni 2/3 mesi ☐ ogni 4/5 mesi ☐ ogni 6/7 mesi ☐ 1 volta all'anno ☐ con minor frequenza

18. Se dovesse esprimere una valutazione sul livello di gravità della CSU di cui soffre questo paziente, che valutazione darebbe?

☐ decisamente grave ☐ grave ☐ abbastanza grave ☐ abbastanza lieve ☐ lieve ☐ decisamente lieve

19. Quali parametri (clinici e non), quali aspetti della patologia ha preso in considerazione per esprimere questa valutazione? Le chiediamo cortesemente di descrivere, brevemente, il razionale che ha seguito per valutare il livello di gravità della malattia _____

20. Questo paziente sarebbe eleggibile al trattamento con il nuovo farmaco di cui le abbiamo mostrato il profilo durante la compilazione del questionario?

☐ Si ☐ No → 20.A **Per quale motivo?** _____

---------- FINE PASSARE ALLA COMPILAZIONE DEL DIARIO PER IL SUCCESSIVO PAZIENTE ----------

STETHOS MARKETING RESEARCH

Patient Diary

CSU Physician Insights quantitative assessment

DEF 25/02/2014
Stethos study code: 131187

Complete Patient Diaries for the last **5 CSU patients you have assessed who are being treated for the condition** (regardless of the type of treatment). Please consider treated CSU patients only and omit patients who are not receiving any pharmacological therapy.

THE PATIENT

1. Sex: ☐M ☐F **2. Age**: |__|__| **3. Year of onset of first symptoms:** |__|__|__|__|

THE DIAGNOSIS

4. Did the patient refer to you directly when he/she developed the first symptoms or only after going to see other physician or the emergency department?

- ☐ directly when he/she developed the first symptoms
- ☐ after going to the emergency department
- ☐after seeing a GP
- ☐ after seeing another specialist → specify which specialist _____
- ☐ don't know / don't remember

5. What assessments/tests did you prescribe when the patient first presented to you with the symptoms? ☐ test1 ☐test2 ☐ test3 ☐ test4 ☐ test5 ☐ test 6 ….

6. Do you remember what symptoms the patient had? ☐ No ☐ Yes_____-

7. Did this patient receive a diagnosis of CSU from you or from another physician? ☐ you ☐ GP ☐ another dermatologist ☐ another allergologist ☐ at the emergency dept. ☐ another specialist → if another specialist _____ please specify _____

8. How long after symptom onset did it take for the diagnosis of CSU to be reached? |__|__| months / |__|__| years

9. In this patient, do the symptoms of CSU re-appear with a certain frequency and regularity?

- ☐ They re-appear frequently and with a certain regularity
- ☐ They re-appear frequently but with no regularity
- ☐ They don't re-appear frequently but they have a certain regularity
- ☐ They don't re-appear frequently and they don't have regularity

9.A How often do the symptoms re-appear? _____open _____

CURRENT THERAPY

10. Current therapy:

- ☐ only H1-antihistamine (standard dose)
- ☐ only H1-antihistamine (increased-dose)
- ☐ H1-antihistamine in combination with H2-antihistamine
- ☐ H1-antihistamine in combination with leukotriene antagonist
- ☐ H1-antihistamine in combination with leukotriene antagonist /H2-antihistamine
- ☐ steroids (alone or in combination with other drugs)
- ☐ systemic calcineurin inhibitors (cyclosporine)
- ☐ another drug / drug combination

11. Date when current treatment was started |__|__|__|__| / |__|__|

12.A The patient's treatment is … ☐ a chronic treatment ☐ an "as needed" treatment (PRN) (the patient takes it when symptoms occur)

12.B Is the patient refractory to his/her current pharmacological treatment? In other words, does the patient continue to have symptoms despite taking the medications?

☐ Yes ☐ No

13. In the past, was the patient given other treatments for CSU?

- ☐ No, no other treatment previously (neither topical nor systemic)
- ☐ Yes, but only topical treatments previously
- ☐ Yes, other systemic treatments (oral or by injection) previously

If other pharmacological treatments (oral or by injection) previously

14. What other treatments was the patient given? Please indicate according to the sequence with which they were prescribed and provide the reasons why the treatments were discontinued.

	Indicate treatment	**Indicate the reasons why it was discontinued**
Treatment 1	☐ only H1-antihistamine (standard dose)	☐ tolerability ☐ inadequate efficacy ☐ on patient's request ☐ poor compliance ☐ to improve patient's QoL ☐ other reason_____
	☐ only H1-antihistamine (increased-dose)	
	☐ H1-antihistamine in combination with H2-antihistamine	
	☐ H1-antihistamine in combination with leukotriene antagonist	
	☐ H1-antihistamine in combination with leukotriene antagonist/H2-antihistamine	
	☐ steroids (alone or in combination with other drugs)	
	☐ systemic calcineurin inhibitors (cyclosporine)	
	☐ another drug / drug combination	
Treatment 2	**Indicate treament**	**Indicate the reasons why it was discontinued**
	☐ only H1-antihistamine (standard dose)	☐ tolerability

	☐ only H1-antihistamine (increased-dose)	☐ inadequate efficacy ☐ on patient's request ☐ poor compliance ☐ to improve patient's QoL ☐ other reason _____
	☐ H1-antihistamine in combination with H2-antihistamine	
	☐ H1-antihistamine in combination with leukotriene antagonist	
	☐ H1-antihistamine in combination with leukotriene antagonist/H2-antihistamine	
	☐ steroids (alone or in combination with other drugs)	
	☐ systemic calcineurin inhibitors (cyclosporine)	
	☐ another drug / drug combination	
Treatment 3	**Indicate treatment**	**Indicate the reasons why it was discontinued**
	☐ only H1-antihistamine (standard dose)	☐ tolerability ☐ inadequate efficacy ☐ on patient's request ☐ poor compliance ☐ to improve patient's QoL ☐ other reason _____
	☐ only H1-antihistamine (increased-dose)	
	☐ H1-antihistamine in combination with H2-antihistamine	
	☐ H1-antihistamine in combination with leukotriene antagonist	
	☐ H1-antihistamine in combination with leukotriene antagonist/H2-antihistamine	
	☐ steroids (alone or in combination with other drugs)	
	☐ systemic calcineurin inhibitors (cyclosporine)	
	☐ another drug / drug combination	

If the patient is currently receiving treatment & this is the first treatment he/she has been given (Q. 13= NO or YES but only topical treatments previously)

15. What reason led you to start this specific treatment consisting of "activate items indicated in Q.10"? _____

If the patient is currently receiving treatment & he/she was given other pharmacological treatments previously (Q. 13=other systemic treatments (oral or by injection) previously)

16. What reason led you to start this specific treatment consisting of "activate items indicated in Q.10"? _____

TO ALL

17. How often do you see this patient? ☐ every month ☐ every 2/3 months ☐ every 4/5 months ☐ every 6/7 months ☐ once a year ☐ less frequently

18. If you were asked to express an evaluation of the level of severity of CSU in this patient, what would your evaluation be?

☐ definitely severe ☐ severe ☐ quite severe ☐ quite mild ☐ mild ☐ definitely mild

19. What parameters (both clinical and non-clinical), what aspects of the condition did you consider when expressing this evaluation? Please briefly describe the rationale you followed to evaluate the level of CSU severity _____

20. Would this patient be eligible for treatment with the new drug presented to you during completion of the survey?

☐ Yes ☐ No → 20.A **Why?** _____

---------- THE END – GO ON TO COMPLETE A PATIENT DIARY FOR YOUR NEXT PATIENT ----------

·STETHOS· MARKETING RESEARCH	Questionario Quantitativo Fase estensiva sui pazienti affetti da CSU	*Draft5 – 23/04/2014* codice studio Stethos: 140320

INTRODUZIONE

Buongiorno!
Stethos è un istituto di ricerche di mercato specializzato nel campo farmaceutico. Attualmente stiamo conducendo uno **studio a livello nazionale sull'Orticaria Spontanea Cronica**, volto a rilevare **l'approccio dei pazienti** nei confronti della malattia ed **eventuali bisogni ad oggi non ancora soddisfatti**. Più nello specifico, l'obiettivo di questa ricerca consiste nel rilevare i bisogni e le opinioni dei pazienti affetti da questa patologia, al fine di coinvolgerlo in prima linea nello sviluppo di nuove attività e servizi a supporto della gestione della patologia di cui soffre e del trattamento seguito.

Si senta libero di esprimere i Suoi pensieri e le Sue opinioni rispetto ai temi che verranno trattati nel questionario. Stethos non rappresenta alcuna delle Aziende Farmaceutiche che verranno eventualmente nominate, per cui non dovrà avere alcuna remora nell'esprimere qualsiasi tipo di opinione o commento.

Precisiamo che nel rispetto della legge sulla privacy (D.lgs. 196/03 e successivi articoli), è libero/a di interrompere l'intervista o evitare di rispondere ad alcune domande qualora lo ritenesse opportuno. Garantiamo inoltre che qualsiasi informazione fornita verrà trattata in forma strettamente riservata ed anonima, senza l'uso di dati personali o altri recapiti.

Le risposte che verranno fornite nel corso di questa intervista saranno, ovviamente, tutelate dalla privacy; solo nel caso in cui dovesse fare riferimento a un evento avverso riscontrato durante o dopo la somministrazione di un farmaco, le chiederemo l'autorizzazione a segnalare il suo nominativo al reparto di farmacovigilanza della casa farmaceutica del farmaco in questione, anche nel caso in cui lei lo abbia già segnalato direttamente all'azienda o al suo medico.
Ogni altra cosa che verrà detta durante l'intervista continuerà a restare anonima e confidenziale.

Innanzitutto la ringrazio per aver accettato di collaborare a questo studio.

Dom. 1) **Lei soffre di Orticaria Spontanea Cronica?**
☐ sì → proseguire con la compilazione del questionario
☐ no → la compilazione è terminata

Dom. 2) **Da quanto tempo soffre di Orticaria Spontanea Cronica? Nel rispondere consideri quando la prima volta si sono manifestati i sintomi dell'orticaria spontanea cronica di cui soffre.**
|__|__| anni

Dom. 3) **In quale anno le è stata diagnosticata la patologia?** |__|__|__|__| anno diagnosi

Dom. 4) **Che terapia segue attualmente per l'Orticaria Spontanea Cronica di cui Lei soffre?**
☐ nessuna terapia
☐ solo antistaminico
☐ antistaminico in combinazione con antileucotrieni (es. Singulair, Montegen, Lukasm, Montelukast Tev)
☐ cortisone/corticosteroidi (da soli o in associazione ad altre terapie)
☐ omalizumab (Xolair)
☐ altro farmaco / altra associazione di farmaci

Dom. 5) **A chi si è rivolto la prima volta in cui le sono comparsi i primi sintomi di orticaria?**
☐ pronto soccorso
☐ medico di base (MMG)
☐ l'attuale Dermatologo che mi ha in cura
☐ l'attuale Allergologo che mi ha in cura
☐ un altro Dermatologo diverso da quello da cui sono in cura oggi
☐ un altro Allergologo diverso da quello da cui sono in cura oggi
☐ altro specialista _____quale _____

Dom. 6) **Dopo quanto tempo dalla comparsa dei primi sintomi si è recato al pronto soccorso o si è rivolto ad un medico, la prima volta?**
☐ subito, appena ho visto i primi segni della malattia
☐ dopo qualche giorno
☐ dopo qualche settimana
☐ dopo 2-3 mesi
☐ dopo 4-6 mesi
☐ dopo circa 1 anno
☐ dopo circa 2-3 anni
☐ dopo oltre 4 anni

☐ non ricordo quando

Dom. 7) **Quali sono stati i sintomi che Le si sono presentati la prima volta e che l'hanno indotta a rivolgersi ad un medico o a ricorrere al Pronto Soccorso?**
Specificare _____

Dom. 8) **Quale medico le ha diagnosticato per la prima volta l'Orticaria Spontanea Cronica? Nel rispondere consideri il medico che effettivamente le ha diagnosticato la malattia, non il medico a cui si è rivolto alla comparsa dei sintomi (che potrebbe anche essere stato un altro medico, diverso da quello che le ha fatto poi la diagnosi).**

☐ il medico del pronto soccorso
☐ medico di base (MMG)
☐ l'attuale Dermatologo che mi ha in cura
☐ l'attuale Allergologo che mi ha in cura
☐ un altro Dermatologo diverso da quello da cui sono in cura oggi
☐ un altro Allergologo diverso da quello da cui sono in cura oggi
☐ altro specialista _____quale _____

Dom. 9) **E dopo quanto tempo dalla comparsa dei primi sintomi le è stata diagnosticata l'orticaria spontanea cronica? Ossia quanto tempo è passato da quando ha avuto i primi sintomi a quando il medico per la prima volta le ha detto di cosa soffriva?**

☐ subito, ai primi segni della malattia
☐ dopo qualche giorno
☐ dopo qualche settimana
☐ dopo 2-3 mesi
☐ dopo 4-6 mesi
☐ dopo circa 1 anno
☐ dopo circa 2-3 anni
☐ dopo oltre 4 anni

☐ non ricordo quando

Dom. 10) **Ora, ogni quanto si ripresentano i sintomi dell'orticaria?**

☐ tutti i giorni
☐ tutte le settimane
☐ ogni 2/3 settimane
☐ ogni mese
☐ ogni 2/3 mesi
☐ ogni 4-5 mesi
☐ circa 1-2 volte all'anno
☐ con minor frequenza

Dom. 11) **Quando le ricompaiono questi sintomi, per quanto tempo durano?**

☐ alcune ore
☐ 1-2 giorni
☐ 3-4 giorni
☐ 5-6 giorni / 1 settimana
☐ 2-3 settimane
☐ 1 mese / 1 mese e mezzo
☐ altro _____ specificare _____

Dom. 12) **Prima di arrivare allo Specialista che la segue attualmente, in passato si è rivolto ad altri Specialisti? Se sì, potrebbe indicarmi a quanti altri Specialisti si è rivolto in passato prima di arrivare all'attuale?**

– No, l'attuale medico è l'unico a cui mi sono rivolto Se NO→ D.16
– Sì, quanti medici prima dell'attuale |__|__| Se SI → D.13

Dom. 13) **Per quale motivo ha cambiato in passato diversi Medici, diversi Centri prima di arrivare all'attuale?**

☐ non ero soddisfatto del personale medico (medico e/o infermieri) del precedente centro
☐ l'attuale centro / l'attuale Specialista è più vicino alla città in cui vivo
☐ nel nuovo centro è possibile seguire terapie innovative che nell'altro centro non potevo seguire
☐ i medici precedenti hanno faticato / impiegato troppo tempo a diagnosticarmi la malattia
☐ i medici precedenti non riuscivano a trovarmi una terapia adatta
☐ altra motivazione _____

·STETHOS· MARKETING RESEARCH	Questionario Quantitativo Fase estensiva sui pazienti affetti da CSU	*Draft5 – 23/04/2014* codice studio Stethos: 140320

Dom. 14) **Per l'orticaria spontanea cronica di cui soffre, ora Lei è seguito/a da …**

☐ Allergologo
☐ Dermatologo
☐ Altro specialista _____

Dom. 15) **Chi le ha indicato o consigliato di rivolgersi al Suo attuale Specialista / al Centro presso cui Lei è in cura?**

☐ medico di base (MMG)
☐ altro Dermatologo
☐ altro Allergologo
☐ altro Specialista
☐ familiare / amico / parente
☐ altra persona_____

Dom.16 solo se Dom.4≠ nessuna terapia & Dom.4≠ omalizumab (Xolair)

Dom. 16) **La terapia che sta seguendo è una terapia che assume al bisogno, ossia che assume solo alla ricomparsa dei sintomi?**

☐ sì
☐ no

Se Dom.16=SI (terapia al bisogno)

Dom.16.A) **Da quanto tempo sta seguendo questa terapia?**

☐ da meno di 1 mese
☐ da 1-2 mesi
☐ da 3-4 mesi
☐ da 5-6 mesi
☐ da 6-12 mesi (da meno di 1 anno)
☐ da circa 1-2 anni
☐ da circa 2-3 anni
☐ da 4 anni o più
☐ non ricordo da quando

Se Dom.16=SI (terapia al bisogno)

Dom.16.B) **Mediamente per quanto tempo segue questa terapia ogni volta che ricompaiono i sintomi della malattia?**

☐ per un solo giorno
☐ per qualche giorno
☐ per 1-2 settimane
☐ per 3-4 settimane / circa 1 mese
☐ per più tempo _____ specificare _____

Dom. 17) **In passato ha seguito altre terapie per cercare di tenere sotto controllo i sintomi dell'orticaria?**

☐ No, nessun'altra terapia in passato (né topiche né orali né iniettive)
☐ Sì, in passato altre terapie topiche_____ specificare _____
☐ Sì, in passato altre terapie orali _____ specificare _____
☐ Sì, in passato altre terapie iniettive _____ specificare _____

Dom. 18) **Ogni quanto si reca dallo Specialista che la segue per l'orticaria, per i controlli e le visite?**

☐ più di una volta al mese
☐ circa una volta al mese
☐ circa una volta ogni 2/3 mesi
☐ circa una volta ogni 4/5 mesi (2 volte all'anno)
☐ circa una volta all'anno
☐ meno spesso / con minor frequenza

Dom. 19) **Dallo Specialista ci va solo al momento del bisogno (ad esempio, quando ricompaiono i sintomi o per problemi sulla terapia) oppure programma per tempo le visite?**

☐ solo al bisogno
☐ visite programmate

Dom. 20) **Quanto si ritiene soddisfatto del rapporto che ha instaurato con lo Specialista che attualmente la segue?**

☐ decisamente soddisfatto
☐ soddisfatto
☐ né soddisfatto né insoddisfatto
☐ insoddisfatto
☐ decisamente insoddisfatto

Dom. 21) **Vorrebbe avere più tempo a disposizione / maggior confronto con il proprio medico oppure, al contrario vorrebbe che queste visite, questi momenti di confronto fossero più sporadici e meno frequenti?**

☐ Sì vorrei più tempo a disposizione / più confronto con il mio medico
☐ No, vorrei che i momenti di confronto fossero meno frequenti
☐ No, mi va bene così / il tempo che mi dedica il medico è sufficiente

Dom. 22) **Attraverso quali canali di informazione si aggiorna / recupera informazioni sulla sua patologia? A chi chiede informazioni?**

□ siti internet dedicati all'orticaria → **Quali?** _____open _____
□ internet in generale → **Quali?** _____open _____
□ forum di discussione online
□ convegni / conferenze
□ documentazione cartacea (riviste / brochure / volantini)
□ associazioni pazienti → **Quali?** _____open _____
□ dermatologo di fiducia / centro di dermatologia presso cui sono in cura
□ infermiere del centro presso cui sono in cura
□ altro
□ nessuno / non mi informo / non chiedo informazioni

Dom. 23) **In base alla diagnosi che le è stata effettuata dal medico, che livello di gravità ha la forma di Orticaria di cui Lei soffre?**

☐ lieve
☐ moderata
☐ severa/grave
☐ il medico non ha indicato il livello di gravità della malattia

Dom. 24) **Quanto impatta sulla sua vita (personale e lavorativa) l'orticaria? Esprima la sua valutazione con un punteggio da 1 a 6**, dove 1 indica che "la malattia non incide in alcun modo sulla sua vita" e 6 che "la malattia incide notevolmente sulla sua vita".

Impatto della malattia sulla sua vita 1☐ 2☐ 3☐ 4☐ 5☐ 6☐

Dom. 25) **Quale tra queste affermazioni riflette maggiormente il suo pensiero sulla orticaria spontanea cronica di cui Lei soffre?**

□ è una malattia della quale subisco le conseguenze
□ è una condizione con cui convivo
□ fa parte della mia vita come altre "cose"
□ è una sfida quotidiana

Dom. 26) **Rispetto al passato, a quando per esempio non era ancora in trattamento oppure seguiva una terapia che però non portava agli effetti desiderati, oggi come è cambiato il suo rapporto ed il suo approccio nei confronti della malattia?**
Rispetto al passato ora va …

□ decisamente peggio □ peggio □ più o meno uguale □ meglio □ decisamente meglio

Dom. 27) **Da un punto di vista economico, quanto è gravosa / impattante la spesa che lei sostiene per le terapie che deve seguire, per i farmaci che deve assumere, per gli esami e i controlli che deve effettuare periodicamente? Risponda cortesemente prendendo in considerazione tutte le**

spese che sostiene per curare l'orticaria di cui soffre, utilizzando un punteggio da 1 a 6 dove 1 indica "nessun impatto economico, in quanto tutto mi viene rimborsato" e 6 indica invece "molto gravoso, l'impatto economico è elevato, in quanto non viene rimborsato nulla e devo pagare tutto".

1☐ nessun impatto economico / tutto è rimborsato da SSN
2☐
3☐
4☐
5☐
6☐ molto gravoso, l'impatto economico è elevato, in quanto non viene rimborsato nulla e devo pagare tutto

Dom. 28) **Cosa le viene rimborsato dal SSN (e quindi non paga) e cosa invece deve pagare di tasca sua? Per ogni voce può barrare entrambe le caselle, nel caso una parte la paga di tasca propria ed una parte le viene rimborsata.**

	Rimborsato da SSN	Pagato di tasca propria
– farmaci	☐	☐
– creme/pomate/unguenti/lozioni	☐	☐
– esami di controllo	☐	☐
– visite dallo specialista/ presso il centro in cui sono in cura	☐	☐

Dom. 29) **Se dovesse indicare qual è o quale è stato l'elemento, l'aspetto della malattia di cui Lei soffre che ha o ha avuto maggiormente impatto sulla sua vita, cosa le viene in mente?**
_____open _____

Dom. 30) **Pensi ora al suo farmaco ideale per il trattamento dell'orticaria di cui Lei soffre. Quali sono le caratteristiche che lei reputa più importanti? Le metta in ordine di importanza, partendo dalla caratteristica più importante ossia quella che Lei ritiene assolutamente fondamentale in un farmaco per la cura dell'orticaria per finire con quella che lei ritiene meno importante.** *(scegliere almeno tre item)*

Il farmaco deve avere … …
- ☐ un'efficacia che duri nel tempo
- ☐ un'azione rapida
- ☐ effetti collaterali sopportabili / tollerabili
- ☐ una frequenza di somministrazione tale da non impattare sulla mia qualità di vita
- ☐ una modalità di somministrazione tale da non impattare sulla mia qualità di vita

Dom. 31) **Quanto sarebbe propenso a seguire una terapia iniettiva che prevede una iniezione 1 volta al mese per un periodo di circa 3-6 mesi? Risponda utilizzando una scala di valutazione da 1 a 10 dove 1 indica "assolutamente NON seguirei una terapia iniettiva" e 10 indica "certamente la seguirei".**

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Dom. 32) **Nel Centro presso cui è in cura, sono messi in atto specifici servizi di supporto al paziente affetto da orticaria spontanea cronica? Se sì, quali?**
☐ NO
☐ SI Dom.32.A) **Quali sono questi servizi?** _____ open _____

Dom. 33) **Presso il Centro in cui è in cura, le hanno mai consegnato dei materiali cartacei relativi alla sua patologia?**
☐ NO
☐ SI → 33.A **Quali argomenti trattavano?**
- ☐ Diari pazienti (es. questionario sulla qualità della vita/ scala valutazione del prurito / dei pomfi)
- ☐ Evoluzione della patologia e sintomi
- ☐ Consigli su alimentazione e stile di vita
- ☐ Terapie
- ☐ Modalità di somministrazione
- ☐ Brochure informative

·STETHOS· MARKETING RESEARCH	Questionario Quantitativo Fase estensiva sui pazienti affetti da CSU	*Draft5 – 23/04/2014* codice studio Stethos: 140320

Dom. 34) **Quali esami, quali controlli deve effettuare periodicamente? Nel rispondere pensi sempre a tutti gli esami che deve effettuare in riferimento alla orticaria spontanea cronica di cui soffre.**

_____ open _____

Dom. 35) **Le chiediamo ora di esprimere una valutazione utilizzando una scala di punteggio da 1 a 10 dove 1 indica una valutazione "decisamente negativa di totale insoddisfazione" e 10 indica invece una valutazione "decisamente positiva, di completa soddisfazione".**

• Tempo di attesa per prenotare una prestazione (esame e/o visita)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Tempo di attesa tra la prenotazione e l'effettuazione della prestazione (esame e/o visita)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Tempo di attesa rispetto all'ora della prenotazione (di un esame e/o di una visita)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Tempo di attesa per il ritiro dei referti	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Informazioni ricevute dal personale medico/sanitario del centro	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Servizi in generale del centro presso cui Lei è in cura	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Facilità/comodità nel raggiungere dalla Sua abitazione il Centro presso cui Lei è in cura	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Numero di medici / infermieri presenti nel reparto/centro presso cui Lei è in cura	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Dom. 36) **In genere, riscontra o ha riscontrato delle difficoltà quando, ad esempio, deve prenotare gli esami o le visite? Se sì, potrebbe indicare cortesemente quali difficoltà o criticità riscontra?**

_____ open _____

Dom. 37) **Quanto Le pesa il doversi recare presso il Centro in cui è in cura per effettuare periodicamente le visite o gli esami? Nel rispondere prenda in considerazione ad esempio, il viaggio che deve sostenere dalla Sua abitazione al Centro presso cui è in cura, al tempo che deve dedicare a questi esami, alla frequenza con cui deve effettuare gli esami … etc etc. Risponda per cortesia con un punteggio da 1 a 10 dove 1 indica "**non mi pesa affatto**" e 10 indica "**decisamente pesante**".**

□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Dom. 38) **Ha qualche idea o suggerimento da proporre o ha in mente qualche servizio particolare che potrebbe essere attivato dal Centro presso cui è in cura o da un'Azienda farmaceutica per rendere più agevole questo aspetto?**

_____ open _____

Dom. 39) **Se fosse disponibile un servizio domiciliare dedicato ai pazienti affetti da Orticaria Spontanea Cronica, che ad esempio la potrebbe agevolare nel reperire i farmaci necessari per la terapia oppure la potrebbe supportare durante l'iniezione del farmaco, nel caso Lei dovesse seguire una terapia iniettiva, quanto riterrebbe utile un servizio di questo tipo? Risponda per cortesia con un punteggio da 1 a 10 dove 1 indica "**assolutamente inutile**" e 10 indica "**decisamente utile**".**

□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Dom. 40) **Ultimissima domanda. C'è qualche servizio, qualche attività, qualche aspetto particolare che Lei ritiene possa essere di aiuto e di sostegno per una persona che come Lei soffre di orticaria spontanea cronica? Nel rispondere pensi a tutti i servizi e agli aiuti di cui ha beneficiato o, al contrario, a tutto ciò di cui ha bisogno o avrebbe avuto bisogno in passato ma che non riceve o non ha ricevuto.** _____ open _____

Siamo giunti al termine. Compili ora la griglia sottostante, con il suo profilo socio-demografico.

Dom. 41) **Lei è …** □ uomo □ donna

Dom. 42) **Quanti anni ha?** |__|__|

Dom. 43) **Come è strutturato il suo nucleo familiare?**

□ vive da solo
□ vive con la sua famiglia di origine (genitori)
□ vive con il suo partner senza figli
□ vive con il suo partner ed ha figli
□ vive da solo con i figli

Dom. 44) **Qual è la sua professione?**
□ Lavoratore dipendente/insegnante
□ Libero professionista/Imprenditore/Professione autonoma
□ Disoccupato/Casalinga/Pensionato
□ Studente
□ Altro

Dom. 45) **Qual è il suo titolo di studio?**
□ Laurea/Master
□ Diploma di scuola superiore
□ Diploma di scuola media inferiore
□ Licenza elementare
□ Nessun titolo di studio

Dom. 46) **Mediamente, in un anno quante volte le capita di lasciare la sua città per vacanze/trasferte/viaggi (comprensivi di almeno 1 notte fuori casa)?**
|__|__| Viaggi/trasferte/vacanze in **Italia**
|__|__| Viaggi/trasferte/vacanze all'**estero**

NOME |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
COGNOME |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
CITTA |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
VIA/PIAZZA |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
NUMERO DI TELEFONO |_|_|_|_|-|_|_|_|_|_|_|_|_|_|_|
INDIRIZZO E-MAIL |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

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·STETHOS· MARKETING RESEARCH

Quantitative Questionnaire

Extensive phase on patients affected by CSU

Draft5 – 23/04/2014
Stethos study code: 140320

INTRODUCTION

Hello!
Stethos is a market research institute specialising in the pharmaceutical sector. We are currently conducting a **nation-wide survey on Chronic Spontaneous Urticaria,** with the aim of understanding **patients' attitudes** to the disease and **any needs that remain unmet**. More specifically, the purpose of the survey is to identify the needs and opinions of patients affected by CSU, in order to involve them directly in the development of new activities and services to support disease's management and treatment.

Please feel free to express your thoughts and opinions with regard to the topics addressed in this questionnaire. Stethos does not represent any of the Pharmaceutical Companies that may be mentioned, so please have no qualms about expressing any type of opinion or comment.

Also note that in accordance with the Italian laws on privacy (Italian Law no. 196/03 and subsequent amendments), you are free to interrupt the interview whenever you want and to avoid to answer to some questions... Moreover, we guarantee that any information you provide will be handled with strict confidentiality and anonymity, without the use of personal data or other contact details.

The privacy of the answers provided in the course of this interview will clearly be safeguarded; only in the case that you should mention an adverse event encountered while or after drug administration, we will askfor your permission to give your name to the pharmacovigilance department of the pharmaceutical company producinnf the drug , even if you have already notified it to the company or to your doctor.
The content of the rest of the interview will continue to remain anonymous and confidential.

Firstly, thank you for agreeing to collaborate in this survey.

Q. 1. Do you suffer from Chronic Spontaneous Urticaria?

- ☐ yes→ continue with the questionnaire
- ☐ no→ terminate the questionnaire

Q. 2. How long have you been suffering from Chronic Spontaneous Urticaria? To answer, consider the first time in which the symptoms of your Chronic Spontaneous Urticaria appeared.
|__|__| years

Q. 3. When the diseasehas been diagnosed (year)? |__|__|__|__| year of diagnosis

Q. 4. Which is your current therapy for your Chronic Spontaneous Urticaria?

☐ no treatment
☐ only antihistamine
☐ antihistamine in combination with leukotriene antagonist (e.g., Singulair, Montegen, Lukasm, Montelukast Tev)
☐ cortisone/steroids (alone or in combination with other therapies)
☐ omalizumab (Xolair)
☐ another medicine / combination of medicines

Q. 5. Who did you seek help from when the symptoms of urticaria first appeared?

- ☐ emergency department
- ☐ my general practitioner (GP)
- ☐ the Dermatologist who is currently treating me
- ☐ the Allergologist who is currently treating me
- ☐ another Dermatologist, different from my current one
- ☐ another Allergologist, different from my current one
- ☐ another specialist _____please specify _____

Q. 6. How long after the appearance of the first symptoms did you go to the emergency department or a doctor for the first time?

- ☐ immediately, as soon as I saw the first signs of the disease
- ☐ a few days later
- ☐ a few weeks later
- ☐ after 2-3 months
- ☐ after 4-6 months
- ☐ after about 1 year
- ☐ after about 2-3 years
- ☐ after more than 4 years
- ☐ I don't remember when

Q. 7. What were your first symptoms that prompted you to seek medical help from a doctor or emergency department?

Specify _____

Q. 8. Which doctor first gave you a diagnosis of Chronic Spontaneous Urticaria? To answer, consider the doctor who actually diagnosed the disease, not the doctor you saw when the first symptoms appeared (this might have been a different doctor from the one who actually made the diagnosis).

☐ the emergency department doctor
☐ my general practitioner (GP)
☐ the Dermatologist who is currently treating me
☐ the Allergologist who is currently treating me
☐ anther Dermatologist, different from my current one
☐ another Allergologist different from my current one
☐ another specialist _____please specify _____

Q. 9. And how long after the appearance of the first symptoms did you receive a diagnosis of Chronic Spontaneous Urticaria? In other words, how long passed between the appearance of your first symptoms and the first time the doctor made the diagnosis?

☐ immediately, at the time of the first signs of disease
☐ a few days later
☐ a few weeks later
☐ after 2-3 months
☐ after 4-6 months
☐ after about 1 year
☐ after about 2-3 years
☐ after more than 4 years
☐ I don't remember when

Q. 10. Now, how often do your urticaria symptoms re-appear?

☐ every day
☐ every week
☐ every 2/3 weeks
☐ every month
☐ every 2/3 months
☐ every 4-5 months
☐ about once/twice a year
☐ less frequently

Q. 11. When these symptoms re-appear, how long do they last?

☐ a few hours
☐ 1-2 days
☐ 3-4 days
☐ 5-6 days / 1 week
☐ 2-3 weeks
☐ 1 month / 1 month and a half
☐ other _____ specify _____

Q. 12. In the past, did you see other specialists before to be in charge of by your current specialist? If so, could you indicate how many other specialists you saw before your current one?

– No, my current specialist is the only one I contacted If NO→ Q.16
– Yes, I saw |__|__| specialists before my current one If YES → Q.13

Q. 13. In the past, why did you change several physicians and center before arriving at your current one?

☐ I was not satisfied with the healthcare staff (physicians and/or nurses) of the previous center
☐ my current center / specialist is closer to the city where I live
☐ in the new center I can be treated with innovative therapies that were not available in the other center
☐ the previous physicians were finding it difficult / were taking too long to diagnose my condition
☐ the previous physicians were unable to find a suitable treatment for me
☐ another reason _____

Q. 14. For your Chronic Spontaneous Urticaria you are currently treated by …

☐ Allergologist
☐ Dermatologist
☐ Another specialist _____

Q. 15. Who indicated or suggested that you should go to your current treating specialist / center?

☐ general practitioner (GP)
☐ another Dermatologist
☐ another Allergologist
☐ another specialist
☐ family member / friend / relative
☐ another person _____

Q.16 only if Q.4≠ no treatment & Q.4≠ omalizumab (Xolair)

Q. 16. Is the treatment you have been taking one that you take "as needed" (PRN) , i.e., only when the symptoms re-appear?

☐ yes
☐ no

If Q.16=YES (as-needed treatment)

Q.16.A) **How long have you been taking this treatment?**

☐ for less than 1 month
☐ for 1-2 months
☐ for 3-4 months
☐ for 5-6 months
☐ for 6-12 months (less than 1 year)
☐ for about 1-2 years
☐ for about 2-3 years
☐ for 4 years or longer
☐ I don't remember for how long

If Q.16=YES (as-needed treatment)

Q.16.B) **On average, for how long do you take this treatment whenever the symptoms of the disease re-appear?**

☐ for 1 day only
☐ for a few days
☐ for 1-2 weeks
☐ for 3-4 weeks / about 1 month
☐ for longer _____ specify _____

Q. 17. In the past, did you take other treatments to try and control the symptoms of urticaria?

☐ No, no other treatment in the past (neither topical, oral or by injection)
☐ Yes, other topical treatments in the past _____please specify _____
☐ Yes, other oral treatments in the past _____please specify _____
☐ Yes, other treatments by injection in the past _____please specify _____

Q. 18. Every how often do you see the specialist who is treating your urticaria, for check-ups and follow-up appointments?

☐ more than once a month
☐ about once a month
☐ about once every 2/3 months
☐ about once every 4/5 months (twice a year)
☐ about once a year
☐ less often / at less frequent intervals

Q. 19. Do you go to see your specialist only when a need arises (e.g., when symptoms re-appear or for problems with the treatment) or do you schedule your visits in advance?

☐ only as needed
☐ scheduled visits

Q. 20. How satisfied are you with the relationship you have with your current treating specialist?

- definitely satisfied
- satisfied
- neither satisfied not dissatisfied
- dissatisfied
- definitely dissatisfied

Q. 21. Would you like to have more time / more interaction with your doctor or, on the contrary, would you prefer these visits, these opportunities for interaction to be more sporadic and less frequent?

- ☐ Yes, I would like more time / more interaction with my doctor
- ☐ No, I would prefer these opportunities for interaction to be less frequent
- ☐ No, I am happy as it is / the time my doctor devotes to me is sufficient

Q. 22. Which information channels do you use to keep up to date / locate information about your condition? Who do you ask for information?

- ☐ internet sites devoted to urticaria → **Which ones?** _____open _____
- ☐ internet sites in general → **Which ones?** _____open _____
- ☐ online discussion forums
- ☐ meetings / conferences
- ☐ paper-based publications (magazines / brochures / flyers)
- ☐ patient associations → **Which ones?** _____open _____
- ☐ trusted dermatologist / dermatology center where I am being treated
- ☐ nurse at the center where I am being treated
- ☐ other
- ☐ none / I don't look for information / I don't ask for information

Q. 23. Based on the diagnosis you have received from your doctor, what level of severity is the form of urticaria you are suffering from?

- ☐ mild
- ☐ moderate
- ☐ severe
- ☐ the doctor hasn't indicated a level of severity of the disease

Q. 24. How much does urticaria affect your life (personal and working life)? Rate its impact from 1 to 6, where 1 indicates that "the disease has no impact on my life" and 6 that "the disease has a considerable impact on my life".

Impact of the disease on your life 1☐ 2☐ 3☐ 4☐ 5☐ 6☐

Q. 25. Which of these statements best reflects your thoughts about your Chronic Spontaneous Urticaria?

- ☐ it's a disease I am suffering the consequences of
- ☐ it's a condition I live with
- ☐ it's part of my life like other "things"
- ☐ it's a daily challenge

Q. 26. Compared to the past, for example to when you were not being treated yet or when you were taking a treatment that failed to provide the desired effects, how has your relationship and your attitude to the disease changed today?

Compared to the past now it is ...

☐ definitely worse ☐ worse ☐ more or less the same ☐ better ☐ definitely better

Q. 27. Financially, how burdensome / impacting are the costs you incur for your treatments, for the medicines you need to take, and for the assessments and tests you need to undergo periodically? Please answer by taking into consideration all of the expenses you incur to treat your urticaria, and giving a score from 1 to 6 where 1 indicates "no financial impact, as everything is reimbursed" and 6 indicates "very burdensome, the financial impact is high, as nothing is reimbursed and I have to pay for everything myself".

1☐ no financial impact / all expenses are reimbursed by the NHS
2☐

3☐
4☐
5☐
6☐ very burdensome, the financial impact is high, as nothing is reimbursed and I have to pay for everything myself

Q. 28. What does the NHS reimburse (so what don't you pay for) and what do you have to pay for out of your own pocket? For each item you can check both boxes if the item is in part paid for out of your own pocket and in part reimbursed.

	Reimbursed by the NHS	Paid for out of your own pocket
– medicines	☐	☐
– creams/ointments/lotions	☐	☐
– follow-up tests	☐	☐
– visits to your treating specialist / center	☐	☐

Q. 29. If you were asked to indicate what is or has been the element or aspect of your condition that has most affected your life, what would come to mind?
_____open _____

Q. 30. Now think about the ideal drug for the treatment of your urticaria. What characteristics do you consider important? Put them in order of importance, from the most important characteristic - i.e., the one you consider absolutely fundamental for a drug used for treating urticaria - to the one you consider least important. *(choose at least three items)*

The drug should have … …
- ☐ long-lasting effectiveness
- ☐ a fast action
- ☐ bearable / tolerable side effects
- ☐ a frequency of administration that does not negatively affect my quality of life
- ☐ a route of administration that does not negatively affect my quality of life

Q. 31. How willing would you be to follow a therapy based on once-monthly injections over a period of about 3-6 months? Answer by giving a rating from 1 to 10 where 1 indicates "I would definitely NOT follow an injection therapy" and 10 indicates "I would definitely follow an injection therapy".

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Q. 32. Does your treating center offer specific services to support patients affected by Chronic Spontaneous Urticaria? If so, which ones?
☐ NO
☐ YES → Q.32.A **What are these services?** _____ open _____

Q. 33. Has your treating center ever given you paper-based material about your condition?
☐ NO
☐ YES → Q.33.A **What kind of material?**
- ☐ Patient diaries (e.g., questionnaire on quality of life / severity scale for itching / hives)
- ☐ Evolution of the disease and symptoms
- ☐ Advice on diet and lifestyle
- ☐ Therapies
- ☐ Route of administration
- ☐ Information brochures

Q. 34. What tests and assessments do you need to have regularly? To answer, think about all the tests you have to undergo in connection with your Chronic Spontaneous Urticaria.

_____ open _____

·STETHOS· MARKETING RESEARCH	Quantitative Questionnaire Extensive phase on patients affected by CSU	*Draft5 – 23/04/2014* *Stethos study code: 140320*

Q. 35. Now we ask you to rate the following aspects, on a scale from 1 to 10 where 1 indicates a "definitely negative rating reflecting total dissatisfaction" and 10 indicates a "a definitely positive rating reflecting total satisfaction".

• Waiting times to book an appointment (test and/or consultation)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Waiting times between the booking and the appointment (test and/or consultation)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Waiting times in relation to the time of the appointment (for a test and/or consultation)	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Waiting times for collection of reports	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Information received from the center's healthcare personnel	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• General level of services of your treating center	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Convenient location/easy access to your treating center from your home	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10
• Number of doctors / nurses working in your treating clinic / center	□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Q. 36. In general, do you encounter or have you encountered any difficulties when, for example, you need to book tests or consultations? If so, could you please indicate what difficulties or issues you have encountered?

_____ open _____

Q. 37. How inconvenient do you find it to go to your treating center for periodic examinations or tests? To answer, take into consideration the journey between your home and the center, the time it takes to do the tests, the frequency with which you have to do them, etc. Please answer by giving a rating from 1 to 10 where 1 indicates "I don't find it at all inconvenient" **and 10 indicates** "I find it highly inconvenient".

□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Q. 38. Do you have any ideas or suggestions or can you think of any particular service that could be put in place by your treating center or a pharmaceutical company to make this aspect easier?

_____ open _____

Q. 39. If a special home-care service were available for patients affected by Chronic Spontaneous Urticaria - for example, to help you find the medicines required for treatment or provide support during injection of the medicine in the event that you require an injection therapy, how useful would you rate this service? Please answer by rating it from 1 to 10 where 1 indicates "absolutely useless" **and 10 indicates** "definitely useful".

□1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Q. 40. The very last question. Is there some service, activity, special aspect that you believe could be of help and support for a person who, like you, is affected by Chronic Spontaneous Urticaria? To answer, think of all the services and forms of support you have benefitted from or, on the contrary, to all the things you need now and aren't being given or would have needed in the past but were not given. _____ open _____

We have reached the end of the interview. Complete the grid below with your socio-demographic profile.

Q. 41. You are ... □ a man □ a woman

Q. 42. How old are you? |__|__|

Q. 43. What's the composition of your family?

□ I live alone
□ I live with my family of origin (parents)
□ I live with my partner without children
□ I live with my partner and have children
□ I live alone with my children

Q. 44. What's your occupation?

- □ Dependent employee/teacher
- □ Freelancer/Entrepreneur/Self-employed
- □ Unemployed/Housewife/Retired
- □ Student
- □ Other

Q. 45. What is your qualification?

- □ Degree/Master's Degree
- □ Secondary school diploma
- □ Middle school diploma
- □ Primary school certificate
- □ No qualification

Q. 46. On average, how many times a year do you leave your town for holidays/business trips/travels (including at least 1 night away from home)?

|__|__| Travels/business trips/holidays in **Italy**
|__|__| Travels/business trips/holidays **abroad**

NAME |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
SURNAME |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
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The interview is over, thank you for your kind cooperation. Best regards

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **The title on page 1 in the main manuscript states the study design:** *"The state of the art of chronic spontaneous urticaria in Italy: a multicenter survey to evaluate physicians' and patients' perspective"*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Please see the abstract from page 2 to 3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Please see the introduction from page 4 to 5**
Objectives	3	State specific objectives, including any prespecified hypotheses **The introduction on page 5 reported:** *"This survey aimed to assess the clinical status of CSU in Italy from the perspective of specialists who treat CSU (dermatologists and allergy specialists) and patients who have the disease. Both the specialists' therapeutic approach and the patients' experiences were assessed, with a focus on potential barriers to diagnosis and treatment that patients with CSU in Italy may experience"*
Methods		
Study design	4	Present key elements of study design early in the paper **Methods on pages 5 and 6 reported:** *"This multicenter Italian survey comprised two questionnaires, one for physicians and one for patients with CSU. Only data from patients and physicians who accepted to be interviewed were collected. The survey was designed by an independent market research company (Stethos Marketing Research, Milan, Italy) and was tested with pilot interviews to specialists. Survey results were also collected and analyzed by Stethos Marketing Research and stratified according to geographical area and hospital/center size. Due to the qualitative nature of these surveys, no inferential analyses were performed. The research was conducted in conformity with the Code of Conduct 2014 of the European Pharmaceutical Market Research Association (EphMRA)."*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods on page 6 reported:** *Data were collected from a sample of physicians, specifically specialists in dermatology or allergy, to assess their diagnostic-therapeutic approach to CSU. Physicians and centers were selected from a proprietary database of Stethos Marketing Research. In order to obtain a good level of confidence, 320 physicians – 160 dermatologists and 160 allergy specialists – from across Italy who were directly involved in the diagnosis and treatment of CSU were*

		enrolled. *Physicians were asked to complete a survey exploring their approach to the management of CSU and also provided completed patient diaries. The survey, consisting of 28 questions, some of them with sub-questions (for a total of 37), was conducted online using a Computer-Assisted Web Interviewing (C.A.W.I.) platform (…).* *The specialists completed online Web Patient Diaries for the last five CSU patients examined during the study reference period. The objective was to collect at least 1000 patient diaries to allow for a robust dataset including information about the diagnosis, the previous and current treatments and the frequency of visits. This sample of interviewees was to be representative of the population of the CSU specialists in Italy, with a maximum margin of error of ±5.3 and a 95% confidence interval (CI).* **Methods on page 7 reported:** *The patient sample was targeted to ensure a good distribution by geographical area and size of the treating hospital. This was achieved by ranking the centers by the number of CSU patients being treated: the centers with the highest number of patients were selected. A random sample of patients with CSU being treated in each of these centers was asked to participate in the survey, before/after a routine assessment at the dermatology/allergy department. Planned enrolment was about 500 patients with CSU (an average of 4–5 patients from each center). This sample of respondents to the patient survey was to be representative of the population of patients with CSU in Italy (0.5–1% of the Italian population), with a maximum margin of error of ±4.2 and a 95% CI.* *The patient surveys were self-administered via a C.A.W.I. system platform, and comprised of 46 questions, some of them with sub-questions (for a total of 50)*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **For physicians and patients' diaries Methods on page 6 reported:** *Data were collected from a sample of physicians, specifically specialists in dermatology or allergy, to assess their diagnostic-therapeutic approach to CSU. Physicians and centers were selected from a proprietary database of Stethos Marketing Research. In order to obtain a good level of confidence, 320 physicians – 160 dermatologists and 160 allergy specialists – from across Italy who were directly involved in the diagnosis and treatment of CSU were enrolled.* **For patients Methods on page 7 reported:** *The patient sample was targeted to ensure a good distribution by geographical area and size of the treating hospital. This was achieved by ranking the centers by the number of CSU patients being treated: the centers with the highest number of patients were selected. A random sample of patients with CSU being treated in each of these*

		centers was asked to participate in the survey, before/after a routine assessment at the dermatology/allergy department.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **For physicians and patients' diaries Methods on page 6 reported:** *The questions explored topics such as characteristics and records of patients with CSU seen in the clinical practice, patient management, treatments used, drivers for therapy, perceived goals, main drawbacks of therapy and the level of knowledge of existing guidelines. (...) The objective was to collect at least 1000 patient diaries to allow for a robust dataset including information about the diagnosis, the previous and current treatments and the frequency of visits.* **For patients Methods on page 7 reported:** *(...) including those where the respondents could provide demographic details, disease characteristics and disease history, rate their QoL and their treatment satisfaction. To investigate the journey of a patient with CSU arriving at a dermatology/allergy hospital center, the survey questions aimed to identify the steps followed and the possible barriers encountered during the diagnostic and therapeutic pathway, and to assess the impact of the condition on the patients' QoL.* **The questionnaires' forms are available as Supplementary material.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Not applicable.**
Bias	9	Describe any efforts to address potential sources of bias **On page 4 has been reported:** *Limitations include those inherent to the survey/questionnaire format, such as subjective bias*
Study size	10	Explain how the study size was arrived at **For physicians and patients' diaries, on pages 6-7 has been reported:** *This sample of interviewees was to be representative of the population of the CSU specialists in Italy, with a maximum margin of error of ±5.3 and a 95% confidence interval (CI).* **For patients on pages 7 has been reported:** *This sample of respondents to the patient survey was to be representative of the population of patients with CSU in Italy (0.5–1% of the Italian population), with a maximum margin of error of ±4.2 and a 95% CI.*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Not applicable.**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Descriptive methodology. No inferential analysis has been performed, as reported on page 5:** *Due to the qualitative nature of these surveys, no inferential analyses*

		were performed.
		(*b*) Describe any methods used to examine subgroups and interactions **Not applicable.**
		(*c*) Explain how missing data were addressed **No method for missing data has been applied**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **Not applicable**
		(*e*) Describe any sensitivity analyses **Not applicable**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Only the questionnaires by physicians and patients who accepted to be interviewed have been recorded.** **For physicians, on page 8:** *In total, 320 physicians (160 allergy and 160 dermatology specialists) from 194 centers in Northern (35.1%), Central (26.8%) and Southern (38.1%) Italy participated in the survey, and collected 1385 online patient diaries.* **For patients, on page 13:** *In total, 537 patient surveys were conducted between May 6, 2014 to June 12, 2014.*
		(b) Give reasons for non-participation at each stage **Not applicable**
		(c) Consider use of a flow diagram **Not applicable**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **For physicians, on page 8:** *In total, 320 physicians (160 allergy and 160 dermatology specialists) from 194 centers in Northern (35.1%), Central (26.8%) and Southern (38.1%) Italy participated in the survey, and collected 1385 online patient diaries. (...) The distribution of allergy and dermatology specialists working in hospital practice (18.8% vs 16.9%), both hospital and private practice (49.4% vs 40.0%), or private practice only (31.9% vs 43.1%), was similar between groups.* **For patients, on page 14** *The patients who responded to the survey (55.7% female) had a mean age of 39 years (median 37 years, IQR 30–46). Mean and median ages were similar between men (mean 39 years; median 38, IQR 31–46) and women (mean 39; median 37 years, IQR 29–46). Almost 84% of respondents were aged 50 years or under (Table 1).* *Table 1. Baseline demographic characteristics of patients with chronic spontaneous urticarial (CSU).* *Characteristic or demographic* — *Patient survey respondents*

		(N=537)
		Gender, n (% patients)
		Female *299 (55.7)*
		Male *238 (44.3)*
		Age group, n (% patients)
		≤30 years *139 (25.9)*
		31–40 years *175 (32.6)*
		41–50 years *135 (25.1)*
		51–60 years *66 (12.3)*
		>60 years *22 (4.1)*
		Geographical region, n (% patients)
		North-West *141 (26.3)*
		North-East *61 (11.4)*
		Centre *106 (19.7)*
		South *229 (42.6)*
		Disease severity, n (% patients)
		Mild *120 (22.3)*
		Moderate *323 (60.1)*
		Severe *56 (10.4)*
		(b) Indicate number of participants with missing data for each variable of interest **Not applicable**
Outcome data	15*	Report numbers of outcome events or summary measures **Not applicable**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Not applicable**
		(*b*) Report category boundaries when continuous variables were categorized **Not applicable**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Not applicable**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Not applicable**
Discussion		
Key results	18	Summarise key results with reference to study objectives **On page 18**: *Highlighting the complexity of the disease itself, 40% of specialists surveyed felt that CSU diagnosis was complex and the difficulty in identifying the cause of the pathology and the multiplicity of tests available for diagnosis were listed as factors contributing to the level of complexity in disease diagnosis.* *(…)* *For most of the allergy and dermatology specialists, the ideal sequence of treatment, at the time of the survey, would be a standard and an increased dose of a non-sedating antihistamine as first-line and second-line treatment, respectively. For third-line treatment for*

		non-responders, specialists tended to favor treatment with an increased dose non-sedating antihistamine in combination with a LTRA and an H2-antihistamine, or an increased dose non-sedating antihistamine in combination with a steroid or cyclosporine, a regimen especially preferred in more severe disease. **On page 19:** *For the specialists surveyed, the main goal of CSU treatment was key symptom resolution (itching and hives) and few considered improving QoL a priority.* **On page 20:** *(...) there was a gap in the knowledge of the specialists regarding the main scales used to assess disease activity, with only approximately half of the surveyed specialists acknowledging familiarity with the UAS and UAS7, and only one-sixth acknowledging familiarity with and utilized the CU-QoL questionnaire* **On page 20-21:** *In their efforts to obtain symptom relief, over a third of patients had on average consulted two previous physicians. Surprisingly, the number of specialists changed did not vary significantly when stratified by disease severity. The most common reason for switching providers was dissatisfaction with medical staff.* **On page 21:** *Furthermore, most patients did not have patient support services available to them at their medical center.*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **On page 21:** *The limitations of the present study include those inherent in the survey/questionnaire format. Although the questionnaires were designed to minimize bias, there is always a subjective element remaining (e.g. respondents tend to avoid scoring at the end of scales and answer in a way they perceive to be desired by the investigator/be more socially acceptable).*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **On page 22:** *In general, patients in Italy with CSU are similar to patients with CSU in other countries. However, there are some gaps in the care of these patients resulting in treatment dissatisfaction and a decreased QoL. These results should be used to improve the treatment of patients with CSU in Italy, in particular by reinforcing the knowledge of the available tools, such as the UAS and CU-QoL questionnaires, which can be used to assist specialists in treating patients with CSU*
Generalisability	21	Discuss the generalisability (external validity) of the study results **On page 21:** *A strength of the study is that, by selecting a representative sample of both patients with CSU and of specialists involved in the treatment of CSU in Italy, it provides a snapshot of the management of this*

		condition from both perspectives
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **On page 24:** *Funding for the conduct of the survey, as well as for medical writing assistance and article processing charges, was provided by Novartis Farma, Italy.*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.