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Therapeutic management of chronic spontaneous urticaria in clinical practice: Results from a pilot survey

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Abstract

Background: The therapeutic approaches to patients with chronic spontaneous urticaria (CSU) differ among health care professionals and may be influenced by many factors.

Objectives: This cross-sectional survey was aimed at evaluating physicians' attitudes regarding therapeutic management of CSU on clinical practice.

Methods: A study-specific questionnaire was administered to a group of physicians (n=21) with a specialist interest in CSU from different areas of Italy (Group A) and also to other physicians (n=25) who manage CSU only occasionally in their clinical activity (Group B).

Results: In case of ineffectiveness of second-generation antihistamines at standard doses, higher doses of the same drug were always or frequently prescribed by most physicians in both groups, and 64% in group B and one third in group A usually increased the dose up to twice.

Old-generation antihistamines were never used in clinical practice by 14% of survey participants in group A and 24% in group B, with the remaining physicians reporting rare or occasional uses. The prescription of systemic corticosteroids appeared to be more common among physicians in group B. The question concerning the use of alternative drugs in refractory CSU produced different answers between the two groups. Costs and access to specialist reference centers were indicated as the most important barriers to the use of medications different from antihistamines.

Conclusions: These preliminary results suggest that therapeutic approaches to CSU seem to be heterogeneous in clinical practice and could be at least in part conditioned by the different medical settings where physicians usually work.

KEY WORDS: Chronic spontaneous urticaria; Clinical practice; Guidelines; Treatment; Antihistamines; Corticosteroids; Omalizumab; Cyclosporine.

Introduction

Chronic spontaneous urticaria (CSU) is a common mast-cell driven disease characterized by the spontaneous occurrence of wheals and/or angioedema for more than 6 weeks [1]. CSU significantly impairs the patients' quality of life, work productivity and daily activities resulting in high psychological, social and economic burdens [2]. It is a heterogeneous disorder whose management can be challenging and frustrating for both physicians and patients.

The therapeutic approaches to CSU patients differ between health care professionals and in various parts of the world and may be influenced by many factors, including physician's clinical experience, medical setting, accessibility to healthcare resources, knowledge of and adherence to urticaria guidelines [3].

The international European Academy of Allergology and Clinical Immunology/ Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO) guidelines have recommended a stepwise approach to the treatment of CSU, delineated in an algorithm, with sequential steps to be implemented depending on the therapeutic response [1]. The pivotal importance of histamine in the pathogenesis of CSU implies the central role of H_1-antihistamines (AHs) in the symptomatic treatment. Second-generation antihistamines (sg-AHs) at licensed doses are the first-line treatment and up-dosed sg-AHs are the second-line treatment. In patients unresponsive to sg-AHs, adding on omalizumab is recommended as third-line treatment, and adding on cyclosporine is suggested as the fourth step. A short course of systemic corticosteroids can be considered for acute exacerbation at any time.

The aim of the present study was to evaluate physicians' attitudes regarding therapeutic management of CSU.

Methods

A cross-sectional survey was carried out between January and March 2019 sending by e-mail a study-specific questionnaire to a selected group of physicians with experience in CSU management from

different areas of Italy. They were asked to provide the information requested in accordance with their everyday clinical practice. The same questionnaire was administered by the same healthcare professionals to other physicians belonging to their teams who manage CSU only occasionally in their clinical practice. Questions covered different aspects of pharmacological treatment of CSU, with emphasis on the management of refractory cases and use of alternative medications different from AHs (the complete questionnaire can be provided upon request).

The majority of the data analysis was performed in a descriptive way. In order to analyse differences between health care professionals based on their level of expertise and knowledge, participants were divided into two groups: CSU experts (group A) and physicians without regular activities of CSU management in their practice (Group B). Statistical analysis was performed using the Fisher's exact test; *P* values ≤ 0.05 were considered statistically significant.

Results

A total of 46 participants (40 dermatologists, 2 allergists, and 4 allergists and dermatologists) completed the survey. They declared to manage CSU patients in different settings, such as dedicated urticaria services (n=18) or non-dedicated services (n=6) within hospital or university clinics, private practice (n=11) and public outpatient clinics (n=8). A few participants reported mixed types of medical settings. In the subgroup of 21 CSU experts (group A), 70% of them stated that the predominant management of CSU patients occurred in dedicated urticaria units. Group B was composed by 25 dermatologists who occasionally managed CSU patients within three principal settings: public outpatient clinics (n=8), private practice offices (n=8) or non-dedicated hospital services (n=6).

The survey results indicated that, in case of ineffectiveness of a first sg-AH at standard doses, higher doses of the same drug were always or frequently prescribed by 86% of group A physicians (the experts) and 92% of group B physicians (non-experts), without significant differences of attitudes between the two groups. Only a minority of respondents did not change the sg-AH (Table I). The sg-

AH was changed by a significantly higher proportion of physicians in group B as compared to group A (64% versus 14%, respectively, *P*=0.0009) (Table I). Dose escalation up to four times the standard dosage of the sg-AH was performed only by a few physicians (one third in group A and 8% in group B), whereas 64% in group B and one third in group A usually increased the sg-AH dose up to twice (Table I).

Old-generation sedating AHs were never used in clinical practice by 14% of survey participants in group A and 24% in group B, with the remaining physicians reporting rare or occasional uses for various reasons (Table II). The most common reasons for using sedating AHs were sleep disturbances and anxiety. Five participants declared to prescribe them when sg-AHs proved to be ineffective.

As concerns systemic corticosteroids (Table III), CSU experts (group A) described their use in clinical practice as rare (38%) or occasional (62%). The use of systemic corticosteroids appeared to be more common among physicians in group B. In fact, 36% of them reported to frequently prescribe corticosteroids (versus 0% in group A, *P*=0.0021) and 16% always used them as the first treatment of CSU. Nearly half of the total respondents indicated acute exacerbations/relevant flares as the leading cause for prescribing corticosteroids.

The question concerning the use of alternative drugs in CSU refractory to AHs gave rise to extremely different answers between the two groups (Table IV). Among CSU experts, 70% of respondents designated omalizumab as the first-choice alternative medication after failure of AHs and 72% cyclosporine as the second-choice alternative drug, with statistically significant differences in comparison with group B. In group B, the preferred alternative drug in case of refractoriness to AHs was omalizumab for 28% of physicians, systemic corticosteroids for 36% and cyclosporine for 32%, , whereas three quarters of respondents reported omalizumab as the second choice among alternative medications. A statistically higher proportion of physicians in group B chose systemic corticosteroids as the preferred alternative treatment. Very few physicians mentioned further alternatives to be used as third-choice alternative treatments.

Costs and access to specialist reference centers were indicated as the most important perceived barriers to treatment of CSU with medications different from AHs (Table V).

Discussion

The international EAACI/GA²LEN/EDF/WAO guidelines recommend a step-by-step approach to the treatment of CSU [1]. The first-line therapeutic step recommended by the guidelines is the use of the sg-AHs, because of the low cost, the worldwide availability and the high-quality evidence for efficacy and safety, documented by several randomized controlled trials.

On the contrary, the international guidelines discourage the use of first-generation AHs for adults and children because of safety problems and risk of drug interactions. However, sedating AHs continue to be over-utilized because of their over-the-counter status, availability and longevity [3]. In a cross-sectional survey study performed in 2009 in German dermatologists, general practitioners and paediatricians working in private practice, 23% of the respondents stated to use first-generation AHs as first-line treatment for CSU [4]. The majority of respondents in our survey declared to use first-generation AHs rarely or occasionally. The most common reasons for using sedating AHs were sleep disturbances and anxiety.

In case of ineffectiveness of sg-AHs at licensed doses, most physicians in our survey claimed to prescribe a different sg-AH with variable frequency, more often among those belonging to group B.

In the guideline therapeutic algorithm, a trial of up to fourfold dose of a sg-AH is suggested as second line. Ever-growing evidence suggests that CSU patients not responding to standard doses of sg-AHs can benefit from updosing of sg-AHs, although positive results have not been uniformly observed [5-7]. Moreover, sg-AH updosing corresponds to an off-label approach. Our survey results showed that, in patients refractory to licensed doses of sg-AHs, an increase in the dose of the same drug previously administered at standard dosage was commonly suggested in clinical practice, although dose escalation up to fourfold was rarely performed. Instead, a double dose was more frequently prescribed, especially by physicians in group B.

As concerns systemic corticosteroids, the international guidelines advised against their long-term use in chronic urticaria and suggested considering only a short course for acute exacerbation at any time [1]. Previous studies that have analyzed large patient databases, thus reflecting the real-life scenario, showed high rates of prescriptions of systemic corticosteroids for CSU in clinical practice [8,9]. Treatment with systemic corticosteroids, generally for short periods and for a maximum of 30 days, was more commonly prescribed by physicians in group B. It is interesting to note that four physicians, all belonging to group B, indicated systemic glucocorticoids as the first treatment of CSU.

A previous study in our sample documented an overall high rate of knowledge of the EAACI/GA²LEN/EDF/WAO guidelines and adherence to such guidelines for the management of CSU in clinical practice [10]. These aspects can influence treatment choices and approaches, resulting in differences between physicians who regularly follow guidelines and those who do not in everyday practice [11]. Early studies revealed that physicians who are familiar with the guidelines are less likely to use first-generation AHs and systemic steroids, suggesting that guideline recommendations may improve the quality of care [4,12].

In patients unresponsive to sg-AHs at standard or higher doses, the third-line treatment recommended by guidelines is the addition of omalizumab, while the addition of cyclosporine is suggested as a further treatment step [1].

With regard to the use of alternative drugs in CSU patients who do not respond to AHs, different attitudes emerged between the two groups in our study, reflecting the diversity of medical settings and access to treatments. It is well known that omalizumab is the only drug indicated for treatment of CSU refractory to AHs. The efficacy and safety of omalizumab have been demonstrated by several randomized controlled trials and real-world experiences [13-18]. However, this drug can be reimbursed in Italy only within selected tertiary referral centers and is prescribed only by physicians working in such centers. This might be the reason for the lower proportion of physicians who chose omalizumab as the first choice among alternative drugs in group B, that included dermatologists mostly working outside tertiary referral centers. This aspect can also justify the propensity among

physicians in this group to prescribe cyclosporine or systemic corticosteroids to patients refractory to AHs.

Costs and access to specialist reference centers were indicated as the most important perceived barriers to treatment of CSU with medications different from AHs. Safety issues were recognized as less important factors influencing the need of alternative medications.

Our study shows several limitations, including the very limited size of the sample and selection bias, as well as the use of a non-validated questionnaire. Moreover, ~~it recruited~~ a preponderant part of dermatologists was recruited. A previous study found differences between healthcare professionals with diverse specialties with regard to guidelines used, diagnostic work-up and management of chronic urticaria [19].

These results however suggest that the different medical settings where physicians usually work can strongly influence therapeutic approaches and implementation of guideline recommendations. Larger studies with representative samples and validated instruments are necessary to corroborate these preliminary findings.

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TABLE I. - *Treatment with sg-AHs for CSU in clinical practice: Approaches in case of ineffectiveness of standard doses.*

	Group A (n=21)	Group B (n=25)	*P* value
Change of the sg-AH			
Never	1 (5%)	2 (8%)	1
Rarely	2 (10%)	0	0.2029
Sometimes	12 (57%)	4 (16%)	**0.0053**
Frequently	3 (14%)	3 (12%)	1
Always	3 (14%)	16 (64%)	**0.0009**
Increase in the dose of the same sg-AH			
Never	0	0	1
Rarely	0	1 (4%)	1
Sometimes	3 (14%)	1 (4%)	0.318
Frequently	6 (29%)	3 (12%)	0.2639
Always	12 (57%)	20 (80%)	0.1172
Maximum dose usually prescribed for updosing			
Up to twofold	7 (33.3%)	16 (64%)	**0.0122**
Up to threefold	7 (33.3%)	7 (28%)	0.7533
Up to fourfold	7 (33.3%)	2 (8%)	0.059

CSU= chronic spontaneous urticaria; sg-AH= second-generation H_1-antihistamine

TABLE II. - *Treatment with sedating first-generation AHs for CSU in clinical practice.*

	Group A (n=21)	Group B (n=25)	*P* value
Use in clinical practice			
Never	3 (14%)	6 (24%)	0.7119
Rarely	14 (67%)	5 (20%)	**0.0029**
Sometimes	4 (19%)	14 (56%)	**0.0409**
Frequently	0	0	1
Always	0	0	1

Main reasons for use (n=37)

insomnia/sleep disturbances 22%

anxiety	22%
ineffectiveness of sg-Ahs	13.5%
nocturnal itch/interference of CSU symptoms with sleep	8%
induction of sedation	5.5%
persistent itch	3%
psychogenic component	3%
not specified	23%

AHs= H_1-antihistamines; CSU= chronic spontaneous urticaria; sg-AHs= second-generation H_1-antihistamines

TABLE III. - *Treatment with systemic corticosteroids for CSU in clinical practice.*

	Group A (n=21)	Group B (n=25)	*P* value
Use in clinical practice			
Never	0	0	1
Rarely	8 (38%)	4 (16%)	0.1067
Sometimes	13 (62%)	8 (32%)	0.0739
Frequently	0	9 (36%)	**0.0021**
Always	0	4 (16%)	0.1093
*Main reasons for use**			
acute exacerbations/relevant flares			50%
angioedema			22%
diffuse and/or giant wheals			17%
as first treatment			9%
refractoriness to AHs			4%
refractoriness to other drugs (various or unspecified)			6.5%
emergency situations			2%
contraindications to the use of cyclosporine			2%
dyspnea			2%
severe CSU with marked impact on the quality of life			2%
not specified			2%
Average duration of treatment ^			
≤ 7 days			12 (26%)
8-10 days			10 (22%)
11-14 days			8 (17%)

> 14 days up to 30 days	10 (22%)
not specified	6 (13%)

* Each participant reported ≥ 1 item; ^ Extremely variable ranges were reported
AHs= H_1-antihistamines; CSU= chronic spontaneous urticaria

TABLE IV. - *Alternative medications for CSU patients unresponsive to AHs in clinical practice.*

	Group A	Group B	*P* value
First choice	(n=21)	(n=25)	
Omalizumab	15 (70%)	7 (28%)	**0.007**
Systemic corticosteroid	2 (10%)	9 (36%)	**0.0449**
Cyclosporine	2 (10%)	8 (32%)	0.0839
Leukotriene antagonist	2 (10%)	-	0.2029
Ketotifene	-	1 (4%)	1
Second choice	(n=18)	(n=16)	
Cyclosporine	13 (72%)	4 (25%)	**0.0149**
Omalizumab	3 (17%)	12 (75%)	0.0994
Systemic corticosteroid	2 (11%)	-	0.4866
Third choice	(n=9)	(n=3)	
Omalizumab	-	2	-
Systemic corticosteroid	2	-	-
Leukotriene antagonist	2	-	-
Azathioprine	2	-	-
Cyclosporine	1	1	-
Metotrexate	1	-	-
Dapsone	1	-	-

AHs= H_1-antihistamines; CSU= chronic spontaneous urticaria

TABLE V. - *Perceived barriers to treatment of CSU with drugs other than AHs.*

Item	%
Costs	69.5
Access to specialist reference centers	63
Tolerability/safety profile	26
Quality of the available evidence	4
Others (to be specified)	
poor experience with biological therapy	2
contraindications to the use of cyclosporine	2
reluctance of patients towards alternative therapies	2
impossibility of prescribing biological therapy within the medical setting	2
Not specified	6.5

Each participant reported ≥ 1 item
AHs= H_1-antihistamines; CSU= chronic spontaneous urticaria