ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 52, N.3, 112-120, 2020

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Clinical experience of a chronic urticaria referral university center

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Key words

chronic urticaria; treatment; antihistamines; urticaria activity score; quality of life

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Doi
10.23822/EurAnnACI.1764-1489.103

Summary

Objective. *Describing routine procedures, clinical profile and evolution of patients treated in a chronic urticaria (CU) reference center of a university hospital.* **Methods.** *Retrospective analysis of clinical records and database of CU patients registered between March 2011 and February 2016 in a reference center. Besides demographic characteristics, disease duration, comorbidities, angioedema, thyroid lab tests, urticaria subtypes, provocation tests, UAS and CUQ2oL scores were recorded. Patients with 3 or more visits were included in analysis regarding the first and last visits, to evaluate pharmacological treatment and differences of UAS/CUQ2oL scores, antihistamines (anti-H1) dosages and need of other medications, according urticaria subtypes.* **Results.** *During the study, 252 patients were attended, 200 with CU, including 162 women, median age 45 years (perc 25 - 75 = 27 - 58) and median duration of symptoms before diagnosis 24 months (perc 25 - 75 = 9 - 60). Regarding the etiology, 166 (83%) patients had chronic spontaneous urticaria (CSU), 34 (17%) had isolated chronic inducible urticaria (CIndU) and 66 (33%), CSU with CIndU. Among the 123 patients followed up for 3 or more visits, first prescription to 106 (86.2%) patients was monotherapy with anti-H1, and associations with other medications were prescribed to 17 (13.8%). At the last visit, 94 (76.5%) received antihistamines, and 29 (23.5%) used associations. Patients with CSU + CIndU + ASST positive need more association of anti-H1 with other medications than patients with CSU + CIndU and only CIndU ($\chi 2 = 7.998$; p 0.01). Between first and last visits, CUQ2oL mean scores changed from 35.7 (± 21.9) to 22.6 (± 21.0) ($Z = -4.833$ $p < 0.000$).* **Conclusions.** *Most of the patients presented CSU, frequently associated with CIndU. There was an improvement in the patients' quality of life during the follow-up period. All patients were treated with antihistamines and there was a great need for doses above the standardized and also for combination with other medications, especially in patients with concomitance of urticaria subtypes..*

Introduction

Urticaria represents a heterogeneous group of diseases mediated by mast cells, in which wheals and/or angioedema occur spontaneously or induced. Chronic urticaria (CU) is defined when symptoms persist for more than six weeks, and is classified as: chronic spontaneous urticaria (CSU), with known cause or not, and chronic inducible urticaria (CIndU) in which identifiable triggering factors are responsible for the development of lesions (1).

Etiological investigation and treatment are a challenge for physicians and patients, since about 50% of patients present CSU due to unknown causes (2), leading to great frustration. First-line treatment is second-generation antihistamines (anti-H1) at licensed dose. However, response to this therapy is not always satisfactory, and further medication is often required (1).

Chronic urticaria interferes with well-being and daily life, causing a decrease in quality of life (QoL) and affecting school, work and leisure activities. Analysis of disease severity and its impact on QoL are indispensable tools in the global evaluation of these

patients (3,4). The follow-up of patients with chronic urticaria in a specialized/reference outpatient clinic enhances the diagnosis and treatment success (5).

There are few studies about chronic urticaria in Brazilian population. Information of demographic and clinical profiles as well as of therapeutic management in our country can be of great value, for researchers and for the daily practice of general practitioners and specialists (6-11).

The aim of this study was to describe the clinical profile and evolution of patients followed up in a chronic urticaria/angioedema outpatient reference clinic at a university hospital in Brazil.

Material and methods

The study was retrospective, based on the analysis of database of patients diagnosed with chronic urticaria (CU) evaluated in the chronic urticaria outpatient clinic of Policlínica Piquet Carneiro, University of Rio de Janeiro State (PPC-UERJ), in the period of March 2011 to February 2016. This specialized unit receives patients referred by the PPC/UERJ general allergy outpatient clinic and other university centers, which are evaluated through a standardized protocol. The diagnosis of chronic urticaria was clinically defined by clinical history with occurrence of erythematous, papular, pruritic, intermittent lesions for a period of more than six weeks, with or without angioedema. Patients referred with other diagnoses as acute urticaria/angioedema, chronic pruritus and dermatitis were not included in the analysis.

After confirmation of the diagnosis, patients were submitted to CIndU provocation tests according to clinical history. Anti-H1 were stopped seven days before testing. For diagnosis of the symptomatic dermographism (SD), FricTest® is placed vertically and a cross path is performed on the volar surface of the forearm, to an extent of approximately 60 mm. A positive response to this test is considered when a pruritic palpable wheal of ≥ 3 mm width is present within 10 minutes after the challenge. For evaluation of cold and heat urticaria, respectively, an ice cube inside a plastic bag and a glass cylinder with hot water at 44 °C are applied to forearm skin for five minutes. The test responses were evaluated 10 minutes after challenge completion, and were considered positive if test site showed a palpable, visible wheal and flare-type skin. Delayed pressure urticaria was evaluated by suspension of a weight rod (diameter 1.5 cm, 2.5 Kg) over volar forearm for 15 minutes, and test response was assessed 6 hours after the end of provocation testing. The presence of a red palpable swelling at the application site was considered positive (12).

Autologous serum skin test (ASST) and autologous plasma skin test (APST) were indicated in patients with urticaria refractory to treatment with standardized dose anti-H1, and that tolerated discontinuation these drugs use 7 days before testing. Venous blood was collected into sterile glass tubes, without accelerator or anticoagulant for serum, and with sodium citrate for plasma. Blood was allowed to clot at room temperature for 30 minutes before separation, which is done with a bench centrifuge at relative centrifugal force of 500 g for 10 minutes. The ASST and APST were performed by intradermal injection of 0.05 ml of serum, plasma and sterile physiological normal saline (NS) and a positive histamine control by skin prick testing (10 mg/ml) in volar forearm. After 30 minutes, the mean of the maximum perpendicular diameters of any red wheal reactions to the ASST, APST and the NS control skin test were calculated. ASST/APST were positive if ASST/APST mean wheal - NS mean wheal ≥ 1.5 mm (13).

The disease severity was assessed by the physician in-clinic urticaria activity score (UAS), a commonly used Patient Report Outcome measure that assesses the key sign (wheals) and symptom (itch) of CSU, in all medical visits. This score was recorded by the patient and evaluated both number of wheals (0 = none; 1 = 1-20 wheals; 2 = 21-50; 3 = > 50) and intensity of itch (0 = none; 1 = mild; 2 = moderate; 3 = intense) in the last 24 hours, on a scale of 0 to 6. The 0 score corresponds to the controlled disease, while 6 score to great intensity disease (1).

Qol was also assessed in all medical visits, through Chronic Urticaria Quality of Life Questionnaire (CUQ_2oL). This tool comprises 23 items, which in the original in Italian are divided into six domains and, in the Portuguese validated version (Brazilian culture), into three: I, sleep / mental state / feeding; II, pruritus / impact on activities; and III, edema / limitations / appearance. (8) The patient should respond taking account into the last two weeks, indicating in a five-point Likert scale the intensity of each item separately, ranging from 1 = "nothing" to 5 = "very much". For each of the three dimensions a score is calculated, and then a total score is given for all dimensions. The score ranges from a minimum of 23 to a maximum of 115, indicating a better and worse overall quality of life, respectively. In order to make scores more meaningful and to permit comparisons between different populations of patients, linear transformations of raw scores indicating the percent of maximum possible score were performed. Thus, the minimum possible score is defined as 0 and the maximum possible score is defined as 100 (8,14).

In addition, thyroid laboratory tests (free T4, TSH, and thyroid autoantibodies [TAA] as thyroid peroxidase antibody [anti-TPO] and thyroglobulin antibody [anti-TG]), which are routinely collected on the suspicion of CU in our service, were requested for all patients.

Besides socio-demographic characteristics as age and gender, the following clinical data was recorded: presence of angioedema, urticaria subtypes (CSU, CIndU), comorbidities (atopic, cardiovascular, psychiatric, rheumatologic, endocrinological and oncological diseases), time between the onset of symptoms and the first medical visit, results of provocation tests, ASST/APST,

thyroid laboratory tests, UAS ratings (scores < 4 and ≥ 4) and CUQ_2oL scores at first consult of all patients with CU attended at the outpatient clinic during the study period. The distribution of results of thyroid autoantibodies and ASST was evaluated, as well as CUQ_2oL scores according to UAS ratings.

Patients with ≥ 3 visits to the urticaria outpatient clinic were included in analysis regarding the first and last visits, to evaluate pharmacological treatment and differences of CUQ_2oL scores, UAS ratings, anti-H1 dosages (on demand and single dose versus up to four times the standard dose) and need for medications associated with anti-H1, according urticaria subtypes (isolated CIndU; CSU + CIndU; CSU + CIndU + ASST positive). We also analyzed frequency of patients who were discharged from the outpatient clinic, who interrupted follow-up, and those who were being followed up in February 2016, and analyzed UAS/CUQ_2oL scores in the first and last visit between patients in follow-up, and who interrupted follow-up, with the objective of evaluating whether severity and impact on quality of life are related to follow-up abandonment.

Descriptive statistics were reported by frequency and means ± standard deviation (SD) and medians (interquartile range [IQR]). Prevalence rates are shown as percentages. The chi-square and McNemar's tests were used to study the relationship between qualitative variables. Non-parametric (Wilcoxon, U-Mann Whitney or Kruskal-Wallis) tests were used to study the relationship between continuous variables. Significance was achieved with $p < 0.05$. Statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Ethical aspects

This study followed the principles of the Declaration of Helsinki and was approved by the Research Ethics Committees of the Institute of Public Health of the University of the State of Rio de Janeiro (Process no. 1.675.616/2017). Confidentiality of data was ensured throughout the study.

Results

During the study period, 252 patients were attended in the chronic urticaria outpatient clinic, 52 of whom had no chronic urticaria (UC). The most frequent diagnoses among these group were chronic pruritus (13), acute urticaria (13), acute angioedema (10), atopic dermatitis (2), contact dermatitis (5) and others (9).

From the 200 CU patients seen at the first evaluation with median age 45 years (IQR 27 - 58 years; range 5 - 82 years), 162 (81%) were female and 29 (14.5%), children. The median time between the onset of urticaria and the first evaluation was 24 months (IQR 9 - 60 months; range 2 - 564 months), 82 (41.0%) had symptoms for less than 1 year, 21 (16.0%) less than 2 years, 40 (20.0%) for 2-5 years and 46 (23.0%) for more than five years.

About 112 (55.0%) patients also complained of angioedema episodes. The most common comorbidities were arterial hypertension in 57 (28.5%) patients, allergic rhinitis in 50 (25.0%), asthma in 19 (9.5%), hypothyroidism in 17 (8.5%), rheumatological diseases in 11 (5.5%), oncological diseases in 8 (4.0%), psychiatric diseases in 7 (3.5%) and atopic dermatitis in 3 (1.5%) (**table I**). Non-steroidal anti-inflammatory drugs triggered urticaria in 29 (14.5%) patients, antibiotics in 7 (3.5%), whereas ACE-inhibitors and dexchlorpheniramine maleate in only one patient each.

Regarding the etiology, 166 (83.0%) patients had CSU and 34 (17.0%) had isolated CindU. Sixty-six (33.0%) patients with CSU presented CindU (**table I**).

All patients underwent provocation tests for dermographism with 86 (43.0%) positive tests, 79 for cold with 8 (10.1%), 78 for heat with 3 (3.8%), 64 for delayed pressure with 7 (10.9%), 76 for ASST with 41 (53.9%), and 72 and for APST with 28 (38.8%).

Thyroid laboratory tests were requested for all patients, but only 146 performed thyroid hormone serum levels (T4 and TSH) and 121 thyroid autoantibodies measurements (anti-TPO and anti-TG). Of these, 15 (10.2%) presented alterations in hormonal levels (8 patients T4 normal and TSH high, 4 patients T4 normal and TSH low, 3 patients T4 high and TSH normal) and 22 (18.2%) positive thyroid autoantibodies (TAA). In a subset of 54 patients submitted to ASST and TAA measurements, it was observed: 30 ASST positive 8 (26.7%) patients with increased TAA serum levels, and 22 (73.3%) normal, and 24 ASST negative, two (8.3%) positive patients with increased TAA serum levels, and 22 (91.7%) normal.

The CUQ_2oL median scores (0 - 100) on the first visit was 26.2 (IQR 13.35 - 44.10; range 0 - 78.62). Physician in-clinic UAS scores < 4 were observed in 171 (85.5%) patients and ≥ 4 in 28 (14.5%), with 88 (44.0%) patients that presented pruritus, and only 48 (24.0%) that had wheals at the time of the first evaluation. The CUQ_2oL scores are high (i.e. worse) in patients with UAS scores ≥ 4 (U 832.000; $p < 0.000$) (**table I**).

Follow-up data

The clinical characteristics of the 123 patients followed by 3 or more medical visits are very similar to the patients seen at least once, as seen in **table I**. Among these patients, 22 were followed-up for less than one year, 50 for one, 23 for two and 28 for three to five years, with median follow-up time of 14 months (IQR 7 - 27 months; range 2 - 58).

Only eleven patients (9%) were discharged due to disease remission, 42 (34%) interrupted the follow-up and 70 (57%) were still under follow-up in February 2016. Patients in remission

Table I *- Sample general and clinical characteristics.*

Characteristics	CU patients (n = 200)	CU patients' follow-up group[1] (n = 123)
Sex, n (%)		
male	38 (19.0)	19 (15.5)
female	162 (81.0)	104 (84.5)
Age, y (median / range)	45 (27 - 58) / 5 - 82	43 (28 - 58)/ 6 - 82
children, n (%)	29 (14.5)	18 (14.6)
adults	171 (85.5)	105 (85.4)
Time of disease in first visit (m) median (IRQ) / range	24 (9 - 60) / 2 - 564	24 (9 - 72) / 2 - 360
< 1 y, n (%)	82 (41.0)	47 (38.2)
1-2 y	32 (16.0)	18 (14.6)
2-5 y	40 (20.0)	25 (20.2)
> 5 y	46 (23.0)	32 (26.0)
Angioedema, n (%)	112 (56.0)	69 (56.0)
Urticaria subtypes, n (%)		
CSU (isolated)	100 (50.0)	53 (43.0)
CSU + CIndU	66 (33.0)	47 (38.2)
CIndU (isolated)	34 (17.0)	23 (18.8)
Autoimmunity, n / total n (%)		
ASST	41 / 76 (53.9)	38 / 63 (60.3)
APST	28 / 72 (38.8)	24 / 60 (40.0)
Thyroid autoantibodies	22/ 121 (18.2)	18 / 94 (19.1)
Comorbidities		
arterial hypertension	57 (28.5)	35 (28.4)
allergic rhinitis	50 (25.0)	28 (22.7)
asthma	19 (9.5)	15 (12.1)
hypothyroidism	17 (8.5)	17 (13.8)
rheumatological diseases	11 (5.5)	9 (7.3)
oncological diseases	8 (4.0)	4 (3.2)
psychiatric diseases	7 (3.5)	2 (1.6)
atopic dermatitis	3 (1.5)	1 (0.8)
Physician in-clinic UAS in first visit, n (%)		
scores < 4	171 (85.5)	101 (82.1)
scores ≥ 4	28 (14.5)	22 (17.9)
CUQ_2oL mean (SD)	n = 160	n = 102
Total	28.6 (20.6)	35.7 (21.9)
UAS scores < 4[2]	25.9 (19.7)[3]	32.4 (21.1)[4]
UAS scores ≥ 4[2]	44.0 (19.0)[3]	49.0 (20.8)[4]

CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; ASST, autologous serum skin test; APST, autologous plasma skin test; UAS, urticaria activity score (0 - 6); CUQ_2oL, Chronic Urticaria Quality of Life Questionnaire (0 - 100); m, months; y, years; SD, standard deviation; IRQ, interquartile range. [1]123 CU patients followed for at least 3 visits. [2]U-Mann Whitney test to evaluated CUQ_2oL scores between patients with UAS scores < 4 and ≥ 4. [3]p < 0.000. [4]p = 0.004.

presented median time of disease progression at the first evaluation of 48 months (IQR 6 - 60 months), follow-up time in our clinic of 21 months (IQR 12 - 30) and disease time at discharge of 72 months (IQR 31 - 83). Among those who remained in follow-up in February 2016, medians were respectively 25 months (IQR 12 - 84), 16 months (IQR 9 - 34) and 54 months (IQR 31 - 101) in the last clinic consultation.

Evaluation of UAS groups (scores < 4; ≥ 4) and CUQ2oL scores between patients who interrupted follow-up and still in follow-up showed no difference between UAS groups and a lower impact on the quality of life at last visit in the patients who interrupted follow-up, (CUQ2oL scores mean at last visit in follow-up group: 28.1 (± 2.9) and in interrupted follow-up group: 15.7 (± 18.4) (U 932.500; p 0.001)

Between first and last visits CU-Q_2oL mean scores changed from 35.7 (± 21.9) to 22.6 (± 21.0) (Z -4.833; p < 0.000), although the physician in-clinic UAS scores demonstrated a less significant change between visits (p 0.04) (**table II**).

On the first visit, patients were treated with anti-H1, 106 (86.2%) as monotherapy and 17 (13.8%) with combination with other medications. In 16 patients (13.0%) the dosage of anti-H1 was on demand, in 56 (45,5%) the maintenance dose was standardized and 51 (41,5%) received up to four times the standard dose (**table III**).

On the other hand, the therapeutic regimen used in the last visit of these patients was anti-H1 monotherapy for 94 patients (76.5%), while 61.8% of them used twofold to fourfold doses, with relevant difference between the two assessments (p 0.008; p < 0.000 respectively) **(table III).** The most frequently prescribed anti-H1 were, in their respective order, cetirizine, hydroxyzine and fexofenadine. Associations with other drugs were necessary in 29 (23.5%) patients, being the most common doxepin (17), followed by oral corticosteroids in short courses for exacerbations (13), montelukast (3), anti-IgE (3) and cyclosporin (2). Seven patients needed association with two or more medications (**figure 1**).

Treatment with anti-IgE and cyclosporin was necessary in five patients, all women with associated angioedema; two had hypothyroidism; one rheumatoid arthritis, and two ASST positivity.

CUQ2oL scores, UAS groups, need of anti-H1 association with other medications and anti-H1 posology in first and last visit according CU subtypes (only CIndU, CSU + CIndU, CSU + CIndU + ASST positive) were evaluated. A tendency to better quality of life in patients with CIndU at the first visit (p 0.07) was observed. In the last visit was observed major association of anti-H1 with other medications in patients with CSU + CIndU +ASST positive ($\chi 2$ 7.998; p 0.01), and a trend not statistically proven for the use of doses above the standard doses in this group of patients ($\chi 2$ 5.558; p 0.06) (**table IV**).

***Table II** - Activity and quality of life evaluation between first and last visit.*

	first visit	last visit	p value
CUQ_2oL, mean (SD), n = 102	35.7 (21.9)	22.6 (21.0)	< 0.000[1]
physician in-clinic UAS, n (%) n = 123			
scores < 4	101 (82.0)	112 (91.0)	0.04[2]
scores ≥ 4	22 (18.0)	11 (9.0)	

UAS, urticaria activity score (0 - 6); CUQ_2oL, Chronic Urticaria Quality of Life Questionnaire (0 - 100); SD, standard deviation. [1]Wilcoxon test. [2]McNemar test.

Discussion

In this study, clinical profile and evolution of CU patients followed-up at a subspecialized university outpatient clinic was described. The patients were admitted with two years of average time of disease and after being treated by several specialists and submitted to many treatments (as about 30% presented symptoms for at least five years), demonstrating the difficulty in appropriate diagnosis and management of this disease (3).

Most of the evaluated patients had CSU, of which 33% associated with CIndU. Maurer et al. (3) evaluated the prevalence and

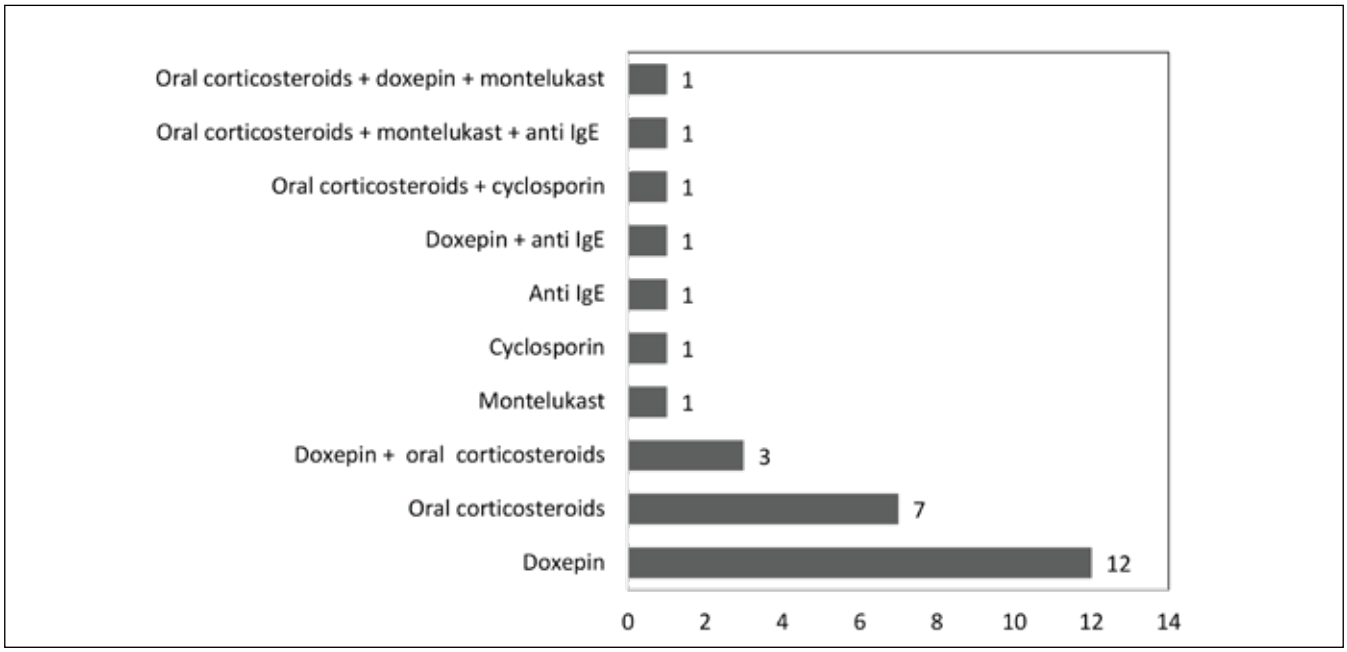
***Table III** - Urticaria pharmacologic treatment at the initial and last visit of follow-up.*

Treatment (n = 123)	first visit	last visit
Medications, n (%)[1]		
anti-H1 only	106 (86.2)	94 (76.5)
ant-H1 + others	17 (13.8)	29 (23.5)
Type of medications, n (%)		
anti-H1		
cetirizine	81 (65.8)	103 (83.7)
fexofenadine	23 (18.7)	30 (24.3)
hidroxizine	20 (16.2)	33 (26.8)
bilastine	9 (7.3)	24 (19.5)
loratadine	3 (2.4)	11 (8.9)
dexclorfeniramine	0	6 (4.8)
desloratadine	2 (1.6)	0
levocetirizine	1 (0.8)	0
ebastine	1 (0.8)	0
others		
doxepin	8 (6.5)	17 (13.8)
oral corticosteroid	11 (8.9)	13 (10.5)
montelukast	1 (0.8)	3 (2.4)
anti-IgE	0	3 (2.4)
cyclosporin	1 (0.8)	2 (1.6)
Anti-H1 dosage, n (%)		
on demand	16 (13.0)	9 (7.5)
single dose	56 (45.5)	38 (30.8)
twofold dose	37 (30.0)	33 (26.8)
threefold dose	5 (4.0)	19 (15.4)
fourfold dose	9 (7.5)	24 (19.5)
Anti-H1 dosage, n (%)[2]		
on demand + single dose	72 (58.5)	47 (38.2)
twofold to fourfold dose	51 (41.4)	76 (61.8)

Urticaria pharmacologic treatment at the initial and last visit of follow-up, in 123 CU patients followed for 14 months (perc 25 - 75 = 7 - 27 months; range: 2 - 58) at least 3 visits.

Anti-H1, antihistamines. [1]p = 0.008 was obtained by comparison between patients treated with only anti-H1 and anti- H1 with other medications in first and last visits. McNemar test. [2]p < 0.000 was obtained by comparison between patients treated with anti-H1 on demand and single doses versus and anti- H1 treated with doses above the standardized. McNemar test.

Figure 1 *- Medications associated with antihistamines in last visit.*



distribution of chronic urticaria in several countries and found that in patients presenting with nonacute urticaria, 66 to 93% had CSU, from 4 to 33% had CindU, and cholinergic urticaria diagnosis varied from 1 to 7%, being the combination of CSU with CindU common. The frequency of CU subtypes in the Brazilian population is still little known. In a study carried out in São Paulo in 2011 with a sample of 62 patients, authors found a frequency of 32.3% of CSU, 27.4% of CindU alone

Table IV *- Chronic urticaria subtypes and evaluation of disease activity/quality of life and pharmacological treatment.*

	first visit				last visit			
	CIndU (n = 23)	CSU + CIndU (n = 24)	CSU + CIndU + ASST (n = 23)	p value	CIndU (n = 23)	CSU + CIndU (n = 24)	CSU + CIndU + ASST (n = 23)	p value
CUQ_2oL (mean/SD)	23.7 ± 15.0	40.0 ± 23.7	38.6 ± 24.2	0.07[1]	16.4 ± 12.6	25.5 ± 22.2	21.0 ± 22.2	0.51[1]
physician in-clinic UAS, n (%)								
scores < 4	21 (91.3)	20 (83.3)	17 (73.9)	0.29[2]	21 (91.3)	21 (87.5)	20 (73.9)	0.88[2]
scores ≥ 4	2 (8.7)	4 (16.7)	6 (26.1)		2 (8.7)	3 (12.5)	3 (26.1)	
Medications, n (%)								
anti H1	23 (100)	22 (91.7)	19 (82.6)	0.10[2]	20 (87.0)	22 (91.7)	14 (60.9)	**0.01**[2]
anti H1 + other drugs	0 (0)	2 (8.3)	4 (17.4)		3 (13.0)	2 (8.3)	9 (39.1)	
Anti-H1 dosage, n (%)								
on demand + single dose	16 (69.5)	13 (54.2)	11 (47.8)	0.30[2]	13 (56.5)	17 (29.2)	17 (26.1)	0.06[2]
twofold to fourfold dose	7 (30.5)	11 (45.8)	12 (52.2)		10 (43.5)	11 (60.8)	12 (73.9)	

CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; ASST, autologous serum skin test; UAS, urticaria activity score; CUQ_2oL: Chronic Urticaria Quality of Life Questionnaire (0 - 100); anti-H1, antihistamines. [1]Kruskal-Wallis test; [2]Chi-square test.

and 40.3% of CSU/CindU association (10). Another study published in the same year in Rio de Janeiro, with 112 patients, showed that 36% of patients presented CSU, 24% isolated CindU and 44% associated CSU/CIndU (8).

Urticaria symptoms are brought about by activated skin mast cells and their subsequent release of histamine and other proinflammatory mediators. The underlying causes and the mechanisms of mast cell activation in most types of urticaria are unknown, and remain to be identified. The presence of IgG autoantibodies against IgE receptors, or IgE and IgE anti-autoantigens as thyroid peroxidase (TPO) on the membrane of basophils and cutaneous mast cells, shows an association between CU and autoimmunity (13,15). ASST/APST are in vivo tests that evaluate autoreactivity, but do not define the diagnosis of chronic autoimmune urticaria. They indicate, when positive, that there may be autoantibodies or other soluble factors potentially involved in the degranulation of cutaneous mast cells. This method should be complemented, if possible, with basophil histamine releasing test and specific IgG autoantibodies against FcεRIa and/or anti-IgE immunoassay to demonstrate antibody specificity (7,13).

Asero et al. have reported that the autologous plasma skin test (APST) is more sensitive than ASST, which was not confirmed by other authors (16-18). In the urticaria outpatient clinic we routinely performed ASST and APST to evaluate the two tests. In the descriptive analysis of this sample we found 53.9% of positivity for ASST and 38.8% for APST. The comparison between the two methods is not the objective of the present research, but a higher positivity of the ASST is observed in our series.

Considering that autoimmune factors may be common features of both thyroid autoimmunity and urticaria, it is likely that both may coexist within the same patient. We found elevated thyroid autoantibodies serum levels in 18.3% patients, that were present in 26.7% of those ASST positive and 8.3% in negative ones. In a systematic review about CSU and autoimmune thyroid diseases, the authors found the frequency of elevated thyroid autoantibodies varying from 3.7% to 37.1% (19).

Among patients followed up in the service for at least three visits, just a small portion was free of disease (less than 10%), with disease time at discharge of 72 months. Van der Valk et al. in a retrospective study with 372 adults identified remission after 5 and 10 years in 29% and 44% of patients, respectively (20). In another retrospective study, Kulthanan et al. revealed that in 337 adults with CSU, 34.5% had remission after 1 year (21). Kozel et al. prospectively measured 220 adults for 3 years and found that 35% of CU patients after 1 year did not present any more symptoms (22). In our study, the disease presented a longer course, which may have occurred because it is a referral service in a tertiary hospital, where the CU duration may be greater.

About 34% patients abandoned treatment, which draws attention to this high dropout rate. Nevertheless, this group had a lower impact on quality of life at the last visit to the service than the patients still in follow-up, which may suggest that the abandonment of the follow-up may be partially related to the improvement or remission of the disease.

The pillars of chronic urticaria management are avoiding triggering factors and pharmacotherapy. The first line treatment is modern second generation anti-H1 in a standardized dose (1), but symptoms improve in less than 50% of patients using this dose (3). Doses above the standard were prescribed for 41.4% of our follow-up group already in the first consultation, since they were previously treated without adequate control, which is a frequent finding in referral services like ours. Anti-H1 monotherapy was instituted in 86.2% of the patients at the first consultation in the follow-up sample, being cetirizine the anti-H1 of choice because of its low cost in our country. As it is available free of charge in public health system, hydroxyzine, a first generation anti-H1 with sedative action, was the second most prescribed antihistamine. Doxepin is a tricyclic antidepressant, which acts through the mixed inhibition of serotonin and norepinephrine recapture, presenting antihistaminic and sedative properties was used in 13.8% of patients (23). In 2014, the AAAAI recommended the use of first-generation anti-H1 or doxepin at night as a third-line treatment of chronic urticaria (24,25). However, in most recent 2017 EAACI/GA²LEN/EDF/WAO guideline, the recommendation for CU treatment is up dosing second generation anti-H1 up to fourfold in patients unresponsive to second generation anti-H1 usual dose. If there is no improvement, it is recommend adding on omalizumab, now their third line treatment proposal.

Regarding treatment in the last medical visit, it was observed that there was a need to increase the standardized dose of anti-H1 in 61.8% of patients and to association with other drugs in 23.5% to achieve control. Patients who present CSU + CIndU + ASST positive need more association of other medication to anti-H1 and also a trend to use doses above the standard doses than patients with only CIndU or CSU + CIndU, showing that patients with ASST positive are more refractory to anti-H1. However, several studies, support that a positive ASST is linked to severe disease, and in our study, we did not find this association (26,27).

Only three patients used anti-IgE until February 2016, since it is available for clinical use in Brazil only since December 2015. Anti IgE access is still a problem in our country and patients frequent request it judicially from the State government or health insurance, because it is not provided by public health services. Currently, 16 patients with refractory CU are on treatment with anti IgE in our Unit.

The use of UAS and CUQ_2oL helps to monitor the evolution of the disease and the efficacy of treatment. The UAS and

CUQ_2oL scores at the first visit were low, due to the heterogeneity of the patients with only 88 (44.0%) patients that presented pruritus, and 48 (24.0%) that had wheals at the first evaluation. The majority of patients' sample analyzed presented mild urticaria activity with low quality of life impairment. However, the evaluation of the CUQ_2oL scores according to UAS showed that patients with higher disease activity have a worse impact on QoL. A significant decrease of CUQ_2oL scores was observed in the follow-up of the patients, which suggests a better control of the disease (28). The analysis of $CUQ_2oL$and UAS according to diagnostic subtypes showed no relevant differences except for a tendency to improve quality of life in patients with CIndU at the first visit. However, it should be mentioned that UAS and CUQ_2oL do not evaluate adequately patients with CIndU, since their questions are not specific for this type of urticaria (29).

The best method for assessing activity is UAS7, since this instrument evaluates the seven days prior to the consultation, evaluating more broadly a disease that has a fluctuating course. Its limitations are the inability to perform at the first consultation and dependence on patient compliance. If UAS7 had been used in the evaluation of the last visit, we would probably have a more accurate analysis of the disease activity. We did not use UAS7 routinely during all period of this study. Only 17 patients answered UAS7 at the last medical visit. Some patients do not understand, and other forget to fill the diary and bring it. About two years ago we regularized the UAS7 use, but the rate of return of this tool has been low, and only patients with more severe disease tend to use UAS7 adequately. Measures to increase adherence to this tool were implemented, and currently the rate of compliance is improving.

Our study had some limitations that must be considered. This study was performed in a single tertiary center; therefore, selection bias might have occurred. It should be considered that is a retrospective study, with analysis of patients' database, and some information as results of thyroid lab tests were not available for all patients. There might be patients with hypo or hyperthyroidism and positive autoantibodies that were not evaluated. Another limitation already mentioned above was a low use of UAS7, which possibly would be a more sensitive tool than physician in-clinic UAS in assessing disease activity. Despite these limitations, we provide useful information regarding the natural course time of CU, disease severity, quality of life and pharmacological treatment prior to the introduction of anti-IgE in chronic urticaria therapy in our country.

Conclusions

Most of our patients presented CSU to which CIndU was frequently associated. All patients were treated with antihistamines and there was a great need for doses above standardized, and also for combination with other medications. We have difficulties in the access to immunobiological therapy, which costs are still a barrier to its use in most of our patients. The disease has a prolonged course and at the time of discharge many patients had symptoms for more than five years. The use of standardized questionnaires for CU have been shown to be important tools to optimize the follow-up and treatment of this challenging disease, which has impact on patients' quality of life. Measures to reduce patients withdraw from treatment and to recover these patients are required in an outpatient clinic specializing in CU.

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