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Latin American chronic urticaria registry (CUR) contribution to the understanding and knowledge of the disease in the region



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ABSTRACT

Chronic urticaria (CU) has a widespread spectrum on causal or exacerbating factors, clinical manifestations, therapeutic response and quality of life affectation. Registries are useful tools in several real-life diagnosis and management approach.

We aimed to evaluate the characteristics of CU patients living in Latin America through an original cross-sectional registry with data entered by regional allergologists.

Results: Three hundred patients were included, being 72% female, with median age of 36 years (1–85) and 20 months of CU median evolution time. The cause of CU was reported as unknown in 72% of them.

Thirty-nine percent of suspected cases presented positive serology for Mycoplasma, positive autologous serum skin test (ASST) was reported in 47%, and occasional presence of thyroid or antinuclear autoantibodies and parasites. The impact of pruritus in their quality of life was moderate to severe in 60% of patients, with almost 3 out of four patients having partial or lack of urticaria control with anti-histamines.

Conclusions: Our registry provides retrospective data on the real-life assistance of a large number of patients from the region. Continuous search for associated conditions and better treatment possibilities are needed, in order to control the significant impact on quality of life and the length of disease.

Introduction

Medical research has shown a huge development in the last decades, particularly based on randomized clinical trials where safety and efficacy of interventions have been objectively demonstrated. However, when the ideal conditions established for efficacy trials intersect with real-world effectiveness evaluations, a gap of information emerges, creating a real need for practicing physicians.

There is also a need for non-interventional data, contributing to

medical knowledge on the natural history or particular aspects of a certain disease, including cost-effectiveness interventions and quality of life.

Registries provide information on several real-life procedures such as diagnosis and management approach or validating outcomes.¹ The quality of evidence a registry could provide has been properly discussed by Dreyer and Garner in the *Journal of the American Medical Association* (JAMA), reporting on the Agency for Healthcare Research and Quality definition of a registry as “an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified

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Abbreviations:

ANA	Anti Nuclear Antibodies
Anti-H1	Anti Histamine 1
ASST	autologous serum skin test
CU	Chronic urticaria
CU-Q2oL	Chronic Urticaria Quality of life Questionnaire
CUR	Chronic Urticaria Registry
CURE	Chronic Urticaria Registry (www.urticaria-registry.com)
ESR	Eritro Sedimentation Rate
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
OR	Odds Ratio
PROs	Patients Reported Outcomes
SLaai	Latin American Society of Allergy, Asthma & Immunology
UAS7	Urticaria Activity Score in 7 days
VDRL	Venereal Disease Research Laboratory

outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose(s)".²

Chronic urticaria is a mast cell driven disease, characterized by the recurrence of wheals, angioedema or both, lasting more than 6 weeks. It impairs quality of life at different levels, and as more is learned regarding the pathogenesis of this chronic condition, there is a need for continual updating of guidelines.³ The heterogeneity in clinical presentation, elicitors and/or causes, therapeutic response and level of quality of life impairment, complicate our ability to develop standardized strategies for the diagnostic and therapeutic approach of this chronic disease.

Based on the above mentioned considerations, members of two Argentinian scientific organizations devoted to research in allergic diseases developed and provided an electronic platform to the Latin American Society of Allergy, Asthma & Immunology (SLaai) for a Chronic Urticaria Registry (CUR). Its characteristics have been previously extensively described and published.⁴ Briefly, allergists from Spanish and Portuguese speaking countries from Latin America registered their cases of chronic urticaria in a retrospective and anonymous manner providing data on demographics, duration of disease, precipitating factors, evaluations performed, validated quality-of-life parameters and treatment response.

Based on previous explanations, here we report on the remarkable findings from a registry of a large sample of patients, potentially providing clues for its approach and management.

Methods

Verified Latin American private and/or public allergologists accessed this restricted online registry through the web page of SLaai and entered anonymous data of patients with chronic urticaria (CU).

Having the classical signs and symptoms for over 6 weeks regardless of cause or provoking factor or previous treatment were the main inclusion criteria; any age or sex was accepted. The background of having had incomplete or temporal control with anti-histamines and controlled co-morbidities was also considered.

Exclusion criteria for registering a case consisted of a change in urticaria condition when co-morbidities were controlled, or complete remission of urticaria when avoiding the identified provoking factors (such as exclusively induced urticaria).

The data requested consisted of age, sex and length of disease by the time of collection of data and identified causes by patients and/or physicians. Also recorded were diagnostic procedures and evaluations performed, laboratory data, treatment received and response. Patient Reported Outcomes (PROs) were evaluated by mean of two validated tools: Urticaria Activity Score in 7 days (UAS7), to evaluate disease activity, and Chronic Urticaria Quality of life Questionnaire (CU-Q2oL), to assess Health Related Quality of Life (HRQoL).⁵⁻⁷

No written consent was required for this observational retrospective study, registering data from the usual management of these patients in an anonymous way by verified physicians.⁸ Notwithstanding, two independent ethics committees were consulted (Medical Council of Salta and Clinical Studies Foundation of Buenos Aires, Argentina); they agreed on this statement, and one of them suggested informing the patient of the initiative and the anonymous feature of the registry if this particular patient assistance was requested again by the reporting physician. This was stated on the web page at the beginning of the registry form.

Descriptive statistics are presented, with frequencies of reported data, comparisons between groups by contingency tables and Yate's χ^2 for the probabilities of a positive test (Interactive Statistical Calculation Pages at www.statpages.info).

Results

At the point when 300 patients had been included (July 2015–May 2018), the authors decided to analyze the collected data. Seventy two percent of patients were female, with a mean age of 36,43 years (age range 1–85).

The list of countries from the region and the participating proportion included: Brazil with 32.3% of reports, followed by Argentina 28%, Venezuela 16.3%, Mexico 9.7%, Dominican Republic 7.7%, Ecuador 3%, Paraguay 1%, and Peru 0.6% as well as Bolivia, Chile, Colombia and Cuba with 0.3% of reports.

The proportion of patients with identified causal agents, yet remaining with urticaria was 28%.

The main results of complementary tests are reported in Table 1. There is no single consensus on CU approach on diagnosis and management.³ Then, total cases for each specific performed test were described in the first row, and positive cases in the next.

From this description, even in a small number of patients we found a high frequency of elevated D dimer. In order to elucidate a statistical difference, a comparison of proportions instead of absolute numbers was performed (62.5% positive vs 37.5% negative), resulting in a significant value of $p < 0.0001$. It also evidenced an Odds Ratio: (OR) = 8 (95%CI

Table 1

Results of complementary tests from 300 patients reported. From this total, the number of patients evaluated on each variable is detailed as N.

Variable	Results
Median evolution in months (range). N = 300	20,5 (1,5–552)
Median serum IgE in KU/L (range). N = 139	144 (1–3245)
Mean eosinophils in % (range). N = 263	2,96 (1–20)
Elevated C Reactive Protein in %. N = 132	32
Positive D Dimer in %. N = 8	62,5
Positive Anti TPO in %. N = 130	9,2
Positive Autologous Serum Skin Test (ASST) in %. N = 87	47,1
Positive ANA in %. N = 114	10,5
Positive VDRL in %. N = 103	1
Positive HIV in %. N = 65	1,5
Positive <i>Helicobacter pylori</i> in %. N = 43	11,6
Positive Mycoplasma in %. N = 33	39,4
Positive HBV in %. N = 77	2,6
Positive Parasites in %. N = 159	8,8
Positive Ice test in %. N = 106	10,4
Positive Vibration test in %. N = 58	0
Positive Local Heat test in %. N = 14	21,4
Positive Pressure test in %. N = 137	21,9

4.01–16.1) to have possible associated conditions such as concomitant angioedema and poor response to AntiH1 antihistamines at double doses.

Among patients reported by their physicians has having a potential identified cause, none of them had physical triggers: in almost 30% (24 patients out of 85) urticaria was associated with drugs (2 patients) as well as with infections (10 cases, reporting 5 with *Helicobacter pilory*, 2 with sinusitis and 3 with genitourinary infections), hypothyroidism (8 cases), stress and chronic gastritis (2 patients each) and food and cryoglobulins (1 patient each). There were 3 patients presenting positive tests for infectious diseases (Cyto Megalo Virus, Ebstein Barr Virus and Staphylococcus in the pharynx), but they were not considered to have a causal role according to the reporting physician's criteria.

Besides, 43.7% of patients having autologous serum test: ASST+ (38 from a total of 87 ASST+) were reported as having autoimmune urticaria as the probable cause ($p < 0.0001$). ASST was positive in 4 out of 6 hypothyroid patients, but antibodies to thyroid peroxidase were found in 9,2% of the patients evaluated for it.

Surprisingly for an endemic region, parasites were found in less than 9% of the samples obtained, having being searched for in around half of the total sample.

Many patients reported with an identified cause (plausible to be an inducible urticaria), had negative tests (pressure, ice, vibration, heat): 21 + out of 85 (almost 25%). When compared with those reported as unknown causes, there were no significant differences ($p = 0.177$).

Data collected from PROs questionnaires showed that 35% of them presented more than 20 wheals, and a larger proportion of 52% had moderate to severe pruritus in UAS7 evaluation. Sixty percent of patients reported having moderate to unbearable pruritus, and 40% presented moderate to unbearable anxiety because of it in CU-Q2oL evaluations (Figs. 1 and 2).

When analyzing representative PROs variables, the mean value of pruritus and the presence of wheals were indicative of a moderate intensity (2.896 points in 1–5 scale), while the mean affectation of sleep, social relationships and work was just over a little (2.15, 2.11 and 2.22 respectively).

Twenty-eight percent of patients had no concomitant angioedema.

On efficacy evaluation of treatment, more than half of patients (61%) had incomplete response to anti-histamines and 10% had no improvement at all. Only 13% could achieve complete control of urticaria with licensed doses of Anti-H1 (Fig. 3).

A descriptive figure with frequencies of treatment provided is shown, where cetirizine was the first choice in almost half of patients, followed by fexofenadine in less than 20% (Fig. 4).

Discussion

The highly relevant value of a registry has been described on introduction, and to our knowledge this is the first publication of data from a chronic urticaria registry. There is a well-known initiative on the topic, the Chronic Urticaria Registry (CURE at <http://www.urticaria-registry.com>), which would certainly provide additional data on this chronic

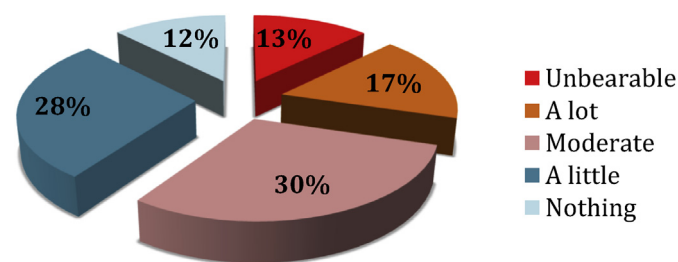


Fig. 1. Impact of Pruritus in the last 15 days, according to validated Quality of Life in Chronic Urticaria questionnaire (CU-Q2oL).

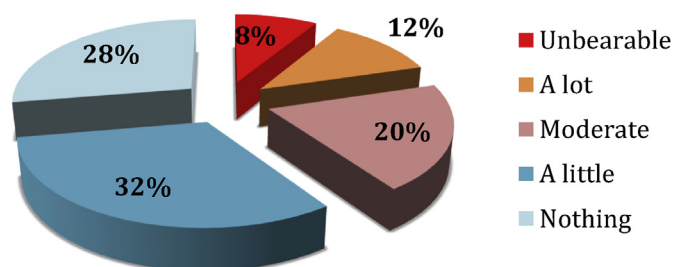


Fig. 2. Level of anxiety feeling associated to chronic urticaria in last 15 days, reported on CU-Q2oL questionnaire.

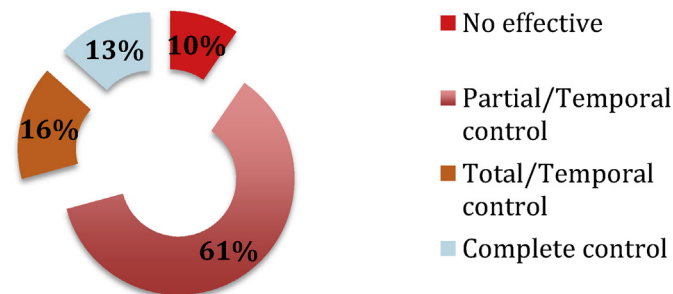


Fig. 3. Efficacy of anti-histamines taken for urticaria control.

condition and particularly on topics that go beyond our present objectives, such as activity and daily impact during the course of disease as well as the attributable health care costs. Our registry provides retrospective data on the real-life assistance of a large number of patients, with a chronic and infrequent condition in the general population, and not of clinical trials or a new intervention under evaluation. This peculiarity allows us to offer an overview of the actual situation of these patients and how they are addressed and treated in daily life in this region.

Our population with 3 out of 4 female patients below 40 years old is not different from previous reports on the topic, and even from predominant age and sex in a smaller Ecuadorian sample.⁹ Surprisingly, coincidentally with this comparison, the median time of evolution of urticaria by the time of assessment in our registry was also above 16 weeks. Even being considered as a chronic condition from 6 weeks onwards, this data about evolution of the entity by the time it is reported in different assessments is far longer, probably suggesting that control of urticaria is not achieved around the moment the diagnosis has been made.

The Latin American region tends to be considered historically as endemic for parasites.¹⁰ However, only in half of patients parasites were searched for and found in less than 10%. A correlation with eosinophilia was considered, but the mean percentage in almost the total sample was below 3%.

Multiple infections were associated with chronic urticaria.^{11,12} From results shown in Table 1, there were minimal frequencies of association with viral infections like hepatitis and HIV, or *H. pylori* infection; there was a remarkable frequency of *Mycoplasma* spp IgG positive test in one third of tested patients. A similar prevalence of 30% of IgM anti *Mycoplasma pneumonia* in acute urticaria, and just 7% in chronic condition, was reported in patients from Singapore, but its role in chronic urticaria remains uncertain¹³. We have previously reported 2 patients having *Treponema* infection and chronic urticaria, which faded out when proper antibiotics were given.¹⁴ The importance of *Helicobacter pylori* presence remains controversial in CU.¹²

Autoimmune factors seem to have a major role in CU, and ASST has been considered an *in vivo* marker of auto-reactivity. Generally, a positive reaction indicates the presence of IgG antibodies against either the high-

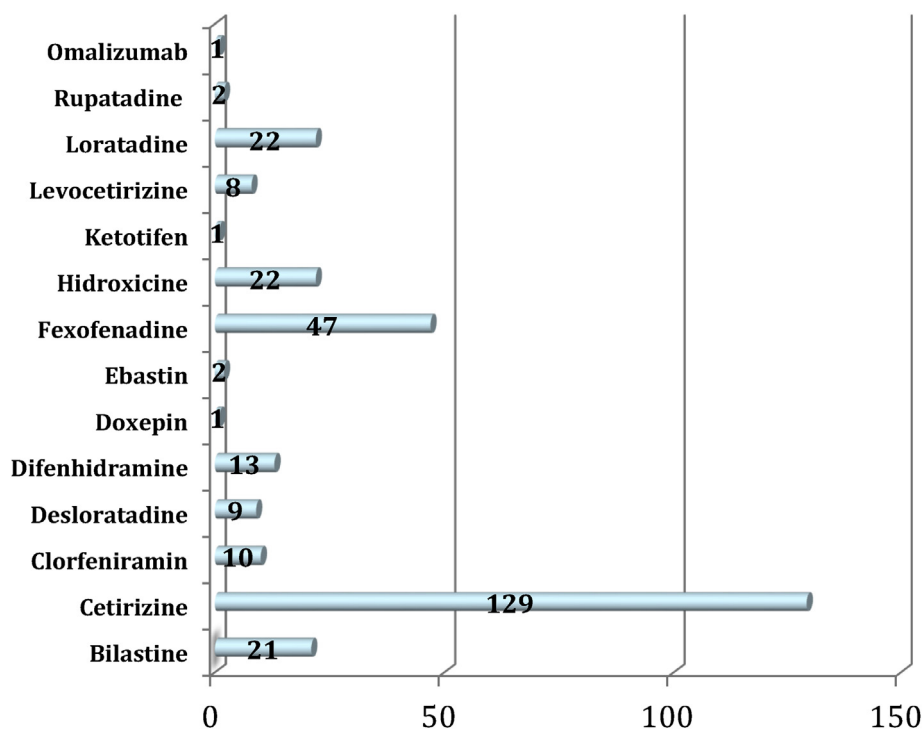


Fig. 4. First choice in prescription of anti-histamines for chronic urticaria treatment (from 288 reports).

affinity IgE receptor (FcεRI) on both mast cells and basophils (in most cases) or membrane-bound IgE (in a minority of patients), with the capacity of inducing basophils or mast cells activation and mediator release. In agreement with a recent Egyptian evaluation and a revision on the pathogenesis of CSU, we found that ASST was positive only in about half of the patients evaluated, despite its severity or length of disease.^{15,16} Not only IgG but also IgE autoantibodies could play a hypothetical role both in the etiology and in pathogenesis of CSU in a subset of patients, such as those having autoimmune thyroid disease, a situation that besides its autoimmune nature, has been termed as “auto-allergic”.^{15,17,18} In the present report we did not have the chance to collect autoantigen-specific IgE, then we found positive IgG anti-thyropoxidase antibodies in less than 10%, and also a similar frequency of antinuclear antibodies. In a large population sample from Israel where antinuclear antibodies were investigated because of autoimmune related symptoms, almost 15% were positive for any Anti Nuclear Antibodies (ANA), and less than 5% presented chronic urticaria.¹⁹ An extended follow-up in such cases was suggested, since a significant proportion of positive patients were diagnosed with an autoimmune disease in a 10-year follow-up evaluation.²⁰

It is speculated that physicians reporting in the present registry consider autoimmunity as one of the identified causes in the reported cases; another possible option of identified cause should be the inducing factors in chronic inducible condition. Nonetheless, only a quarter of physical tests were positive.

Another unidentified association with CU corresponds to the coagulation system involvement. Tissue factor is over expressed in activated eosinophils, and also eosinophilic mediators including tissue factor can activate mast cells.^{15,21} The activation of the coagulation cascade may reflect endothelial cell activation at least in a proportion of patients with chronic urticaria, having elevated D-dimer and being associated, together with other systemic inflammatory markers such as ESR and C Reactive Protein, with higher severity and refractoriness to anti-H1 therapy.^{21,22} In the reduced number of our patients who underwent to D-dimer determination, more than half presented elevated levels, and those were associated to a higher frequency of concomitant angioedema

and lack of control with antihistamines. Besides D-dimer, IL-6 and Lipocalin 2 have been described as serum markers that potentially predict therapeutic response.²³

Regarding therapeutic response, our patients had complete control of urticaria in response to licensed doses of antihistamines in less than 15% of cases, and more than 60% had poor control. The more frequent therapeutic option for our physicians was cetirizine, which is an over-the-counter medication in many places, followed by fexofenadine. It should be mentioned that here we do not have a frame based on the current guidelines indication of a four-fold increase in dose,³ and most of our reported cases used double doses and some antihistamine combinations. For it these reasons, and because the registered report was done at initial evaluations when diagnosing the patient, we only have a single report of omalizumab treatment.

It is also worthwhile to notice the HRQoL involvement at this evaluation time, with 60% of patients having moderate to severe symptoms and almost half of them presenting extreme anxiety. In the present registry, both validated UAS7 and CU-Q2oL tools have been considered (not all variables included from last one, selected at authors' criteria).^{24,25} The significant impact of CU in quality of life has been repeatedly described,^{3,26} and a recent evaluation in a Latin American population from Mexico demonstrated (in coincidence with our results) that pruritus is perhaps the most representative problem, with sleep, social relationships and work also affected.²⁷

No discrimination, neither about private and public assistance nor socio-economic status, was requested on the questionnaire. As a consequence, the impact of these conditions in the evaluated population cannot be inferred.

Conclusions

This analysis of a representative sample of Latin American CU patients provides an overview of the situation of those patients, both for the assisting allergists and for health authorities.

The magnitude of this affection deserves special attention in order to alert physicians, but also to help patients to achieve urticaria control and improve their affected quality of life.

Declarations

Consent for publication

All authors agreed their consent for publication.

Competing interests

There are no Competing interests for the present manuscript.

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