Original Article

Investigation of Patient-Specific Characteristics Associated with Treatment Outcomes for Chronic Urticaria

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What is already known about this topic? Many patients with chronic urticaria (CU) respond to H1-antagonists, H2-antagonists, and/or leukotriene-modifying agents, but others require alternative agents. Limited information is available regarding patient-specific characteristics associated with response to different combinations of treatment.

What does this article add to our knowledge? This article provides useful information regarding treatment response to a spectrum of medications and disease-specific characteristics associated with poor, partial, or complete CU control.

How does this study impact current management guidelines? Results are discussed in the context of the urticaria Joint Task Force Practice Parameter. Although a significant number of patients can be controlled using step 1-4 therapies, there is still an unmet need for novel therapies to control hives.

BACKGROUND: Identifying clinical characteristics of patients with chronic urticaria (CU) responsive to medication may help guide clinicians select treatment.
OBJECTIVE: The objective of this study was to investigate patient characteristics and medication use associated with urticaria control.
METHODS: A retrospective longitudinal chart review of adult patients with CU was conducted at a multisite allergy practice. Inclusion criteria required at least 4 CU office visits to allow for pre- and posttreatment assessment. Control corresponding to medication(s) used was assessed each visit. Univariate analysis followed by multiple logistic regression was performed.
RESULTS: A total of 221 patients with CU were included; 140 (63%) achieved complete control. The average time to control was 1.4 ± 2.7 years, which required 1-3 classes of medications. Dermatographia odds ratio (OR) = 1.85 (95% CI 1.3-2.7) or other physical urticarias, OR = 1.51 (1-2.4) and neutrophilic infiltrates on skin biopsy were markers of poor control. Thyroid autoantibodies were associated with better control using an H1-antihistamine. Whereas 22% were controlled on a second-generation H1-receptor antagonist plus a leukotriene receptor antagonist (LTRA), an additional 33% were controlled when cyclosporine was added. Use of a first or second H1-antagonist or LTRA was associated with a 3.5-16.9 times higher odds of complete CU control in those with dermatographia. The odds of achieving control for other forms of physical urticaria was greatest when colchicine was added (aOR = 32.6 [12.7-83.2]).
CONCLUSIONS: Patient-specific CU characteristics associated with medication-disease control may be useful for selecting treatment regimens. A subset of CU patients remains poorly controlled that indicates an unmet need for novel therapeutic agents. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: *Chronic urticaria; Hives; Patient-specific clinical characteristics; Treatment selection; Control; Physical urticaria; Dermatographism; Medications*

Chronic urticaria (CU) is defined as urticaria that has been continuously or intermittently present for at least 6 weeks and it affects between 0.5% and 5% of the world's population, and up to 1% of the US population.[1-3] CU has a significant impact on patient quality of life, and the associated morbidity and economic burden associated with this chronic intermittent or persistent disease are substantial.[3-8] In fact, the annual economic burden of CU is estimated to be $244 million, the majority of which is due to direct costs related to medications.[3] These costs are even more significant when one considers that the treatment of CU may be required over many years.[9] CU remains a therapeutic challenge for physicians, because there are no well-structured clinically effective treatment

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Abbreviations used
CU- Chronic urticaria
JTFPP- Joint Task Force Practice Parameter
LTRA- Leukotriene receptor antagonist
OR- Odds ratio

algorithm(s) available, based on the presence or absence of specific patient characteristics.[1,10,11] Although the most recent Joint Task Force Practice Parameter (JTFPP) for CU recommends an algorithmic approach (step 1-4) for the treatment of CU, it does not link the step care approach to *objective patient-specific* characteristics (physical, serologic, or histologic traits).[1]

A limited number of studies have tried to identify CU phenotypes based on skin histopathology, the presence of serum autoantibodies, or basophil reactivity in an adult population.[12-14] However, none of these characteristics have reliably been able to be used to predict disease severity or response to treatment resulting in control that could help guide the treating physician in the management of these often challenging patients. In fact, there have been very few retrospective or prospective studies that have tried to identify the *patient-specific clinical* characteristics associated with control of CU in an adult population.[15,16] A practical way to identify clinical characteristics of patients with CU is to determine the medication(s) that are associated with their symptom control.

The primary intent of this study was to identify patient-specific characteristics (ie, gender, age, disease duration, prior medications used, serologic or histologic markers, etc.) of patients with CU associated with their response to treatment. We hypothesized that patient-specific clinical characteristics elicit a response to certain class(es) of mediation(s), and are significantly associated with control of disease in an adult population compared with those who do not achieve control of disease symptoms.

METHODS

Study design

A longitudinal chart review of patients 18 years or older evaluated at a tertiary care outpatient allergy clinic from January 1, 1991, to January 1, 2011, was conducted. Patients were identified with the ICD-9 diagnosis codes of 708.0-708.5, 708.8, or 708.9 for CU. Those who had at least 4 or more clinic visits for CU with a complete medical record that would allow for assessment of pre- and posttreatment courses were eligible to be randomly selected for this study. Patients with urticarial vasculitis and acute urticaria were excluded. It was predetermined that a convenience sample of 220 patient charts would be sufficient for identifying relevant clinical characteristics associated with treatment response based on a previous study that assessed demographic, laboratory, and clinical patterns of a cohort of patients with CU.[15] The total number of charts reviewed to sequentially obtain 221 charts that met predefined entry criteria was 500. Data were collected for patient demographics, medication use, and treatment response at each clinic visit, serologic testing, skin biopsy histology, and family history. Two reviewers extracted information from charts; approximately 10% of the charts (22/221 charts) reviewed by one reviewer were cross-reviewed by a second reviewer to ensure consistency of data extraction and data entry. If there was >10% discordance between the reviewers, the chart was reviewed and queries were resolved by the Principal Investigator (PI). In this circumstance, the PI reviewed the chart, made a decision that resolved the discrepancy(s), and then met with both reviewers to ensure that there was consensus on this determination. This chart review was approved by the University of Cincinnati Institutional Review Board.

Outcome definitions

Complete control of CU was defined as no hives for at least 30 days on medications *and* at least one of the following criteria: the first visit when no new medications were added (ie, a step-up in therapy was not required) *or* the first visit where a step-down in medications was made. *Partial control* of CU was defined as a decrease in the frequency and/or severity of the urticaria episodes after the initiation or change of medication(s). *Remission* of CU was defined as no hives for 3 months off all medications.

Statistical analysis

Demographic and laboratory characteristics were analyzed using descriptive statistics. Univariate analyses were performed by Pearson χ-square tests or unpaired Student *t*-tests to evaluate associations or differences, respectively, between patient baseline and health characteristics and urticaria control status (complete control vs not controlled). Patient characteristics were dichotomized before analysis for ease of interpretation. Patients with partial control of CU were placed in the not controlled category. All factors significant in the univariate analysis at $\alpha = 0.05$ were included in an initial multiple logistic regression model. From this model, patient characteristics were identified by backward selection of *P*-values. The characteristic judged to have the smallest influence, as defined by the *P*-value, was removed and the process repeated on the remaining characteristics, until a final model was determined that could not be improved in a single-step fashion. The *P*-value threshold for the remaining predictors was <.05 or was determined by minimization of the Akaike information criterion. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Data extracted from the charts of a total of 221 patients with CU were included in this study. An extra chart was inadvertently reviewed because it was not clear to the 2 reviewers that the target number of 220 chart reviews had been achieved and therefore included in the final analysis. There were discrepancies between the reviewers in 10 of the 22 charts (10% of charts) that were cross-reviewed related to interpretation of outcome definitions that were reconciled by the PI after the review of the charts and discussion with the reviewers. In all of these cases, to avoid any bias or inconsistencies, the most stringent definitions of outcomes were applied.

The average number of clinic visits per patient was 11.9 ± 9.4. Table I summarizes the basic demographics of the study cohort. A significant majority of the subjects were female (n = 165 [74.7%]), and their mean age at the time of the first clinic visit was 41.1 ± 11.9 years, which was significantly less than that of male patients. The majority of subjects were Caucasian (n = 157 [83.5%]) who had suffered from CU for an average of 3.2 ± 6.9 years before their first clinic visit. Of the 221 patients included in this study, 140 (63.4%) achieved complete control during any point in time of their longitudinal clinical assessment period. Of these, 88 (62.9%) remained completely controlled at their last clinic visit. Only 27 (12.2%) of the 221 patients met our outcome definition of disease remission that was defined as