Original Article

Clinical Control of CSU with Antihistamines Allows for Tolerance of NSAID-Exacerbated Cutaneous Disease

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What is already known about this topic? A large number of patients with chronic spontaneous urticaria (CSU) experience exacerbations after nonsteroidal anti-inflammatory drug (NSAID) intake. International management guidelines propose that patients with CSU avoid NSAID use; however, this can be quite difficult for patients.

What does this article add to our knowledge? The use of antihistamines can allow for clinical control of CSU and prevent NSAID-exacerbated reactions in patients with CSU.

How does this study impact current management guidelines? The use of antihistamines prevents NSAID-exacerbated reactions in many patients with CSU, so their continued use could remove the need for NSAID restrictions. Challenge tests can be used as a diagnostic tool for NSAID reactions and to confirm whether antihistamines induce tolerance to NSAIDs.

BACKGROUND: Many patients with chronic spontaneous urticaria (CSU) experience exacerbations after the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), with clinical implications for the selection of therapeutic options for pain management. Case reports suggest that antihistamines could prevent these reactions.
OBJECTIVE: To determine whether antihistamines can prevent NSAID-exacerbated reactions in patients with CSU.
METHODS: Data on 121 patients with CSU and a history of NSAID exacerbations were evaluated. Two types of challenge with NSAIDs were performed using the NSAIDs reported in the medical record (a diagnostic challenge test without the use of antihistamines and a challenge test using antihistamines). The order in which the tests were performed in each patient was dependent on the treating physician. Patients with a positive first diagnostic challenge underwent a second challenge using H1-antihistamines (anti-H1), patients with a negative first challenge using anti-H1 underwent a second diagnostic challenge without the use of anti-H1, and patients with a negative first diagnostic challenge or a positive first challenge using anti-H1 did not undergo a second challenge. In some patients, additional challenges were performed with an alternative NSAID before performing the diagnostic challenge test or the challenge test using anti-H1.
RESULTS: In the diagnostic challenge test, 96 patients tested positive. Seventy-two (75%) of these patients tolerated the NSAIDs involved in the reaction when they used antihistamines.
CONCLUSIONS: NSAID restrictions create many inconveniences for patients with CSU. Clinical control of CSU with the use of antihistamines can prevent further exacerbations due to NSAID intake in many patients to help them avoid unnecessary restrictions. © **2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Acetylsalicylic acid; Angioedema; Challenge test; Drugs; Hypersensitivity; Hives; Nonsteroidal anti-inflammatory drugs; Urticaria*

INTRODUCTION

Urticaria is a common cutaneous disease. Its chronic form affects around 1% of the general population and has a significant impact on the patient's quality of life.[1] Chronic spontaneous urticaria (CSU) can appear at any time and, for this reason, patients frequently report different foods, drugs, and activities as possible causes of exacerbations.[2,3] Although many

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Abbreviations used
anti-H1- H1-antihistamines
COX1-inh- Cyclooxygenase 1 inhibitor
CSU- Chronic spontaneous urticaria
NSAID- Nonsteroidal anti-inflammatory drug

self-reported triggers have no clinical relevance,[4,5] nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to exacerbate urticaria (NSAID-exacerbated urticaria) in 10% to 30% of patients with CSU.[6,7]

The GA^{2}LEN/WAO/EAACI guidelines[1,8,9] recommend that patients avoid identified triggers; however, patients may find it difficult to adhere to the restrictions on cyclooxygenase 1 inhibitors (COX1-inhs). Most cases of NSAID reactions occur with strong COX1-inhs. Alternative NSAIDs, such as weak COX1-inhs or selective COX2-inhs, are possible substitutes. However, these NSAIDs are sometimes insufficiently effective, and patients with multiple NSAID reactions are frequently intolerant to weak COX1-inhs.

Hives and angioedema are treated successfully with H1-antihistamines (anti-H1) in 30% to 60% of patients with CSU.[10,11] Some reports suggest that different premedication regimens could allow patients with chronic urticaria and a history of NSAID reactions to tolerate these anti-inflammatory drugs.[12-15] The results of these studies support the hypothesis that patients with CSU and a history of NSAID reactions could tolerate NSAIDs once they have clinical control over the disease.

In this cross-over study, we evaluated whether patients with CSU and clinical control (Urticaria Activity Score for 7 days ≤ 6) over the disease using antihistamines had a lower frequency of NSAID reactions during a challenge test.

METHODS

Study design

We conducted a cross-over, multicenter, and ambispective study in 3 clinical centers in Medellín, Colombia. The aim of the study was to determine whether the use of antihistamines can prevent NSAID reactions in patients with CSU. Patients were questioned about NSAID reactions and the involved drug.

According to the study's design, 2 types of challenges with NSAIDs were performed using the NSAIDs reported in the medical record (a diagnostic challenge test without the use of antihistamines and a challenge test using antihistamines). The order in which the tests were performed in each patient was dependent on the treating physician (Figure 1). Patients with a positive first diagnostic challenge underwent a second challenge using anti-H1, patients with a negative first challenge using anti-H1 underwent a second diagnostic challenge without the use of anti-H1, and patients with a negative first diagnostic challenge or a positive first challenge using anti-H1 did not undergo a second challenge.

In some patients, challenges were performed with an alternative NSAID before performing the diagnostic challenge test or the challenge test using anti-H1.

For the diagnosis of NSAID reactions, we used the NSAIDs involved in the previous reaction or acetylsalicylic acid. Some patients underwent a challenge test with a therapeutic alternative (usually weak COX1); however, only patients with at least 1 positive NSAID challenge test result were included in the analyses. If the test result with the therapeutic alternative was negative, a subsequent test was performed with the NSAIDs involved in the previous reaction or acetylsalicylic acid.

Study population

We included patients who were older than 12 years, had been diagnosed with CSU, and had a history of NSAID-exacerbated urticaria. CSU was defined as the spontaneous recurrence of hives, with or without angioedema, for more than 2 days per week and persisting for at least 6 weeks. The exclusion criteria were diagnosis with a systemic disease that could explain urticaria; use of systemic corticosteroids during the 3-week period before the challenge test; and immunodeficiency, dermatitis, and/or any other disease that could alter the interpretation of the challenge test results.

Data were obtained both retrospectively and prospectively. Retrospective data were obtained from patients with CSU who had undergone a challenge test with NSAIDs during the period from January 2017 to December 2018. Additional diagnostic challenge tests or challenge tests using antihistamines were performed on each patient according to the purpose of the study. We also actively recruited patients with CSU who experienced an NSAID exacerbation during 2019 from the 3 centers. Written informed consent to perform the challenge test was obtained from each study participant. The institutional review board of the "IPS Universitaria" clinic approved the study.

Challenge tests

We used a single-blinded and placebo-controlled oral challenge test. NSAID challenge tests were performed on all patients using the same protocol. The placebo consisted of 2 empty capsules that were administered 1 hour before NSAID administration. Thirty-eight patients reported itching due to the placebo; the itching disappeared in less than 20 minutes. No patients experienced hives during the observation period. The equivalent to the maximum daily dose of the drug was administered in 2 doses (10% and 90%, respectively) with a 1-hour interval. In patients who were suspected of having a severe reaction (eg, anaphylaxis or respiratory distress), the administration of the daily dose was divided into 4 steps (10%, 20%, 30%, and 40%, respectively) with a 1-hour interval between steps. After the final dose was administered, patients were observed at the clinic for a period of 2 hours and instructed to notify the clinic if a delayed reaction occurred outside of the observation period. The same protocol was used in all cases of NSAID administration.

The result of the challenge was considered to be positive only in the presence of objective symptoms on the skin or other organ during the challenge test. If, after the first administration of the medication, it was unclear whether the patient had a reaction, the treating physician divided the subsequent dose into a maximum of 4 doses and administered them with an interval of 1 hour between administrations.

For the NSAID challenge tests without the use of anti-H1, patients with CSU were required to suspend their use of this medication for 1 week before the test took place. For the NSAID challenge tests using anti-H1, each patient with CSU continued with their anti-H1 use at either the conventional or a higher dose depending on the dose needed to achieve clinical control (Urticaria Activity Score for 7 days ≤ 6) over the disease.

One of the advantages of the cross-over design was that it allowed each patient to assess their response to challenge with NSAIDs with and without antihistamines. This allowed us to have high confidence that any observed tolerance to NSAIDs was due to antihistamine use. To reduce the likelihood that a reaction was

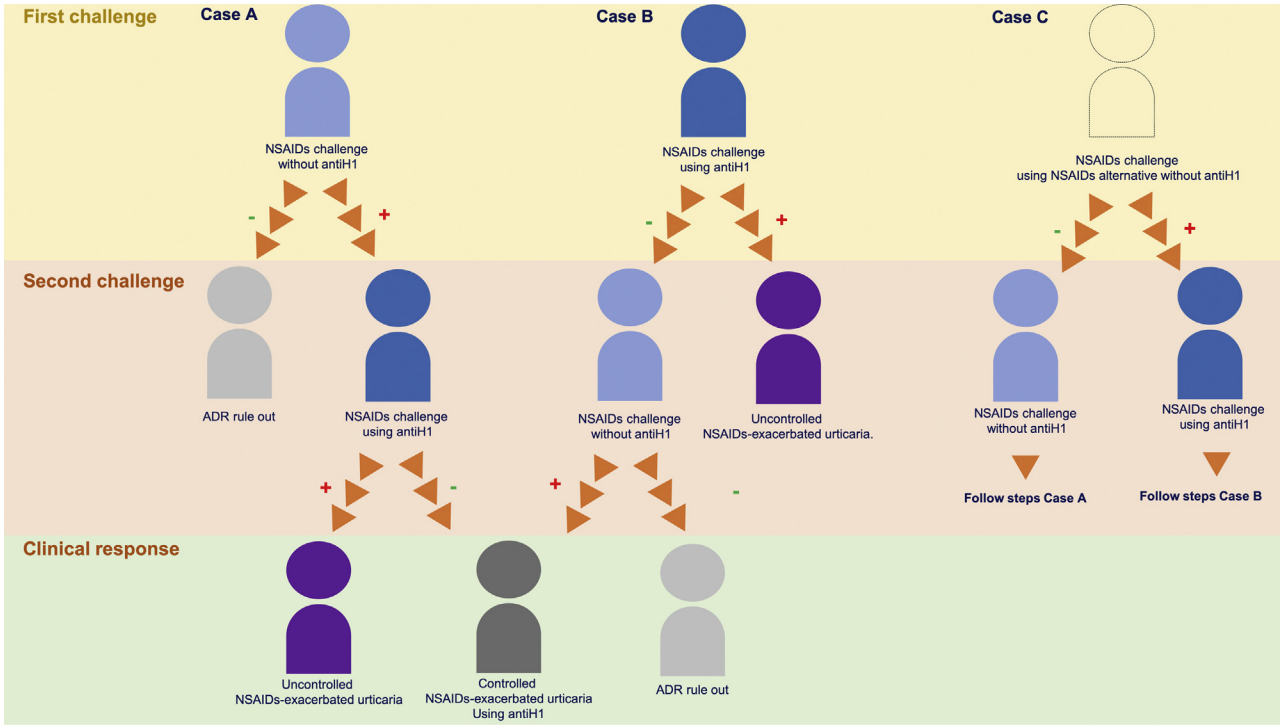

FIGURE 1. Cross-over design. The evaluation carried out for each patient according to the characteristics of the first NSAID challenge with or without antihistamines. *ADR*, Adverse drug reaction.

caused by a spontaneous exacerbation of urticaria, patients were assessed for disease activity 1 week before the challenge test based on the number of hives (hives severity score) and the intensity of pruritus (itch severity score). If, during the previous week, a patient had multiple hives (hives severity score 7 > 7) or intense itching (itch severity score 7 > 7), the challenge test was postponed. On the day of the test, each patient should have had a maximum Urticaria Activity Score of 2 (an itch severity score of <2 and a hives severity score of 0).

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics for Windows program, Version 21.0 (IBM Corp, Armonk, NY). Measures of central tendency and dispersion are presented using the mean and SD, respectively. To compare the results of NSAID challenge tests with antihistamines to those of NSAID challenge tests without antihistamines, we used the Wilcoxon nonparametric statistical test. Given the sample size reported in previous studies that checked for the presence of reactions to drugs in patients with CSU[3,6,7] and the size effect observed for antihistamines,[10,16] we considered that a sample of at least 49 patients would be adequate to guarantee a power of 90% and an alpha error of 0.05 for the measurement of primary outcome. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

Patient characteristics

Data on 121 patients with CSU and NSAID reactions who underwent NSAID challenge tests were evaluated (Figure 2). Although many of the patients had good clinical control of their urticaria (Urticaria Activity Score for 7 days < 6), they still reported occasional relapses with spontaneous hives and itching at least 1 day per month. Twenty-two patients tolerated oral challenge with the NSAIDs reported in their medical history; so, they were excluded from the study (Figure 2).

Ninety-nine patients were tested using antihistamines; however, 3 of these patients were subsequently found to have had a negative diagnostic challenge, so they were considered to not have NSAID-exacerbated urticaria (Table I). Most patients reported a history of reactions to strong COX1-inhs (n = 80 [72%]). The average time between the adverse reaction to the drug and the first challenge test was 9 months (range, 4-12 months). At baseline (before treatment for CSU), the UAS was 3 ± 1.

NSAID challenge tests without antihistamines

A total of 204 diagnostic challenge tests were done without the consumption of antihistamines (173 before and 31 after challenge with NSAIDs using anti-H1) (Table II). Of these, results for 141 (69.1%) were positive. During the challenge tests, 14 patients reported, in addition to skin symptoms (hives and/or angioedema), respiratory symptoms and 2 required the use of adrenaline. Of the 115 challenge tests with a strong COX1-inh, results for 113 (98.2%) were positive. Of the 68 challenge tests with a weak COX1-inh, results for 27 (39.7%) were positive. Of the 21 challenge tests with a selective COX2-inh, result for only 1 (4.7%) was positive. Seventy-seven (34.3%) of the 204 challenge tests were performed with an alternative NSAID; of these, results for 38 were positive and for 39 were negative. Most of the positives occurred when using a weak COX1-inh, and most of the negatives occurred when using a selective COX2-inh.

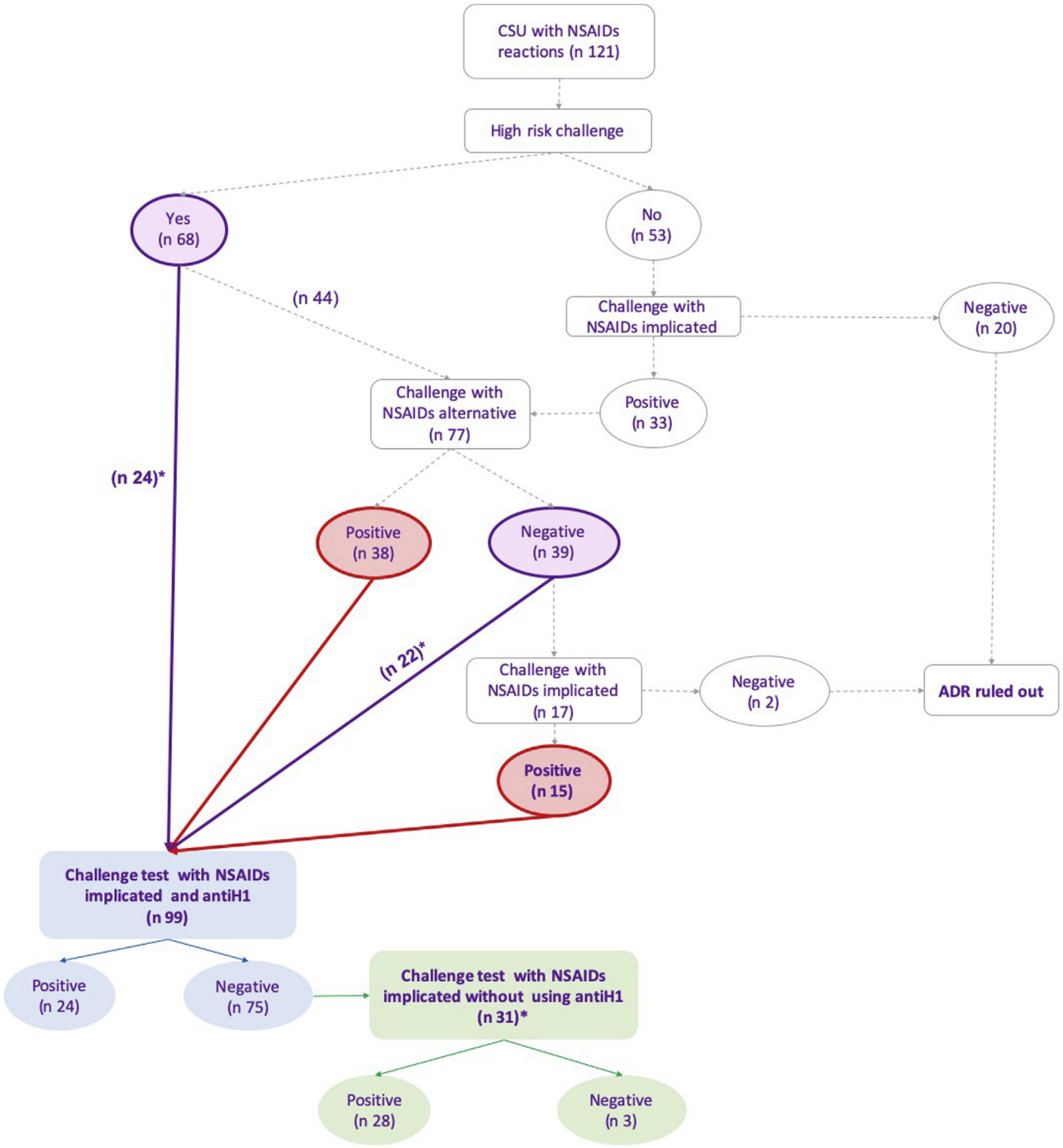

FIGURE 2. Flowchart. A total of 99 patients underwent an NSAID challenge test using anti-H1 (the box and blue circles). These patients were chosen from those with a positive NSAID diagnostic challenge test result or a medical history suggestive of NSAID reactions. *Patients marked with purple (n = 46) are patients with a history of NSAID-exacerbated urticaria but without confirmation using an NSAID diagnostic challenge test. These patients were first challenged with an NSAID with antihistamines; if the challenge was negative, a diagnostic challenge was subsequently performed with the same NSAID but without antihistamines (the green box and circles). *ADR*, Adverse drug reaction.

NSAID challenge tests using antihistamines

A total of 99 NSAID challenge tests were performed while the patients were using antihistamines (Table III). Of the 76 challenge tests with a strong COX1-inh, results for 55 (72.3%) were negative. Of the 20 challenge tests with a weak COX1-inh, results for 18 (90%) were negative. Of the 3 challenge tests with a selective COX2-inh, results for 2 (66%) were negative (Table III). Of the patients with a positive challenge,

TABLE I. General characteristics

Patient characteristics	N = 96
Age (y)	28 (18-52)
Sex: female, n (%)	70 (72.9)
Atopy, n (%)	58 (60.4)
Asthma, n (%)	18 (18.7)
Age at onset of CSU (y)	24 (15-48)
Baseline Urticaria Activity Score, mean ± SD	3 ± 1
No. of NSAID reactions ± SD	1 ± 2
Age at onset of NSAID reactions (y)	27 (18-51)
Last NSAID reaction before challenge (mo)	9 (4-12)
NSAID reactions	111*
Strong COX1-inh (n = 80 [72%])	
Acetylsalicylic acid	18
Ibuprofen	28
Diclofenac	34
Weak COX1-inh (n = 28 [25.2%])	
Acetaminophen (paracetamol)	2
Meloxicam	11
Nimesulide	15
Selective COX2-inh (n = 3 [2.7%])	
Celecoxib	1
Etoricoxib	2

*Some patients could have had more than 1 reaction.

10 presented with respiratory symptoms in addition to cutaneous symptoms and 2 required adrenaline.

Three of the 99 patients tolerated the NSAID reported in their clinical history without the use of antihistamines (Figure 2). Therefore, data for the remaining 96 patients who tested positive in the NSAID challenge test without the use of antihistamines were used to achieve the main objective of the study. With the use of antihistamines, 72 (75%) patients tolerated NSAIDs that they did not tolerate during the diagnostic challenge test ($P < .01$).

Patients received different antihistamines at the dose necessary to achieve clinical control over the disease (fexofenadine [n = 28], desloratadine [n = 26], bilastine [n = 20], cetirizine [n = 12], levocetirizine [n = 8], and rupatadine [n = 2]) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). There were no significant differences between antihistamines or doses regarding the results of the challenge tests.

Some patients underwent their first challenge while on antihistamines, and other patients underwent their first challenge while off antihistamines. The differences in the order in which the tests were performed could be associated with a selection bias. However, we did not find differences between the groups formed by the order in which the tests were performed when evaluating the severity of the reaction to the NSAID, the time of the reaction, or the severity of the urticaria.

DISCUSSION

Hypersensitivity to NSAIDs is present in approximately 10% to 30% of patients with CSU. According to the guidelines, a restriction on the whole family of NSAIDs is the basic recommendation.[1] However, NSAIDs are frequently used because of their analgesic and antipyretic effects. Alternatives may be more expensive and are sometimes less effective. Therefore, the restriction on NSAID use in patients with CSU may have a great impact on a patient in addition to the impact that CSU produces.

Some researchers have attempted to solve this dilemma. Pérez et al[13] observed in 12 patients with NSAID-induced urticaria that pretreatment with antileukotrienes induced complete blockade of the reaction in 3 patients and partial blockade in 6 patients after a challenge test with a strong COX1-inh (ibuprofen). In another report, Trautmann et al[14] observed that the consumption of antihistamines 30 minutes before challenge with an NSAID prevented new reactions in 17 (80.9%) of 21 patients with a history of NSAID reactions (some with NSAID-induced urticaria and others with NSAID-exacerbated urticaria). Asero[12] observed in 87 patients with NSAID-induced urticaria that pretreatment with cetirizine prevented urticaria induced by "alternative" NSAIDs. However, he did not test the tolerance of these patients to the NSAID involved in the previous reaction or a strong COX1-inh.

Despite the small sample size and some limitations to the methodology, these results open the door to the safe treatment of hypersensitivity to NSAIDs. The use of antihistamines as the basic treatment in patients with CSU for the prevention of NSAID-exacerbated reactions has the advantage that it does not generate additional risks or costs.

In our study, we wanted to reproduce previously reported results in a greater number of patients with CSU in whom NSAID reactions had been verified using a challenge test. We observed that, among patients with CSU using antihistamines, 75% tolerated the NSAID involved in the previous reaction and even a strong COX1-inh. This result supports previous observations and may motivate us to reconsider the recommendations in the guidelines regarding NSAID restrictions.

Several antihistamines were administered in different doses (the conventional or a higher dose) (Table E1). Patients with more severe or refractory symptoms usually receive the highest doses of anti-H1. However, our results indicate that the main predictor of tolerance to NSAIDs is clinical control and not a particular type of anti-H1 or the dose. It would be interesting to determine whether those patients who did not tolerate the NSAID at the conventional dose of anti-H1 could tolerate it at a higher dose of anti-H1. Our results suggest that the use of antihistamines and clinical control over CSU could induce tolerance to NSAIDs. If our results are specific to antihistamines or due to clinical control over the disease, this could be clarified by carrying out a study similar to the one described here but with patients who obtained clinical control using another medication (eg, cyclosporine or omalizumab).

The results of this study raise some additional questions. Why does clinical control over CSU allow patients to tolerate NSAIDs? Could anti-H1 be a treatment alternative for patients with NSAID-induced urticaria? These questions, although different, may have a common explanation. Some studies have found that most patients tolerated NSAIDs before the onset of CSU.[17-19] Atopy is common among patients with CSU and NSAID-induced urticaria or asthma.[20,21] Genes implicated in IgE-mediated allergic inflammation, including those regulating IL-4, IL-5, and IL-13 production, are localized in the 5q22−q35 chromosomal region of human chromosome 5, close to the leukotriene-4 synthase gene, and have been implicated in NSAID reactions.[22,23] This colocalization could explain the relationship between urticaria, atopy, and hypersensitivity to NSAIDs, suggesting common elements in the pathogenesis of these processes.

TABLE II. NSAID challenge tests without antihistamines

NSAID challenges without anti-H1	Total no. of NSAID challenges: 204 (100%)	(+) challenges: 141 (69.1%)	(−) challenges: 63 (30.9%)
Strong COX1-inh (n 115)			
Acetylsalicylic acid (1000 mg)	51	49	2
Ibuprofen (1000 mg)	34	34	0
Diclofenac (150 mg)	30	30	0
Weak COX1-inh (n = 68)			
Acetaminophen (1000 mg)	17	4	13
Meloxicam (15 mg)	21	3	18
Nimesulide (175 mg)	30	20	10
Selective COX2-inh (n = 21)			
Celecoxib (300 mg)	15	1	14
Etoricoxib (105 mg)	6	0	6

The challenge tests are grouped according to the result (columns) and the used NSAID (rows).

TABLE III. NSAID challenge tests using antihistamines

NSAID challenges with anti-H1	Total no. of NSAID challenges using anti-H1 (n = 99)	(+) challenges: 24 (24.2%)	(−) challenges: 75 (75.7%)
Strong COX1-inh (n = 76)			
Acetylsalicylic acid (1000 mg)	15	3	12
Ibuprofen (1000 mg)	27	7	20
Diclofenac (150 mg)	34	11	23
Weak COX1-inh (n = 20)			
Acetaminophen (1000 mg)	2	0	2
Meloxicam (15 mg)	9	1	8
Nimesulide (175 mg)	9	1	8
Selective COX2-inh (n = 3)			
Celecoxib (300 mg)	1	0	1
Etoricoxib (105 mg)	2	1	1

The challenge tests are grouped according to the result (columns) and the used NSAID (rows).

Among the strengths of our study is that we performed the diagnostic challenge tests with the medication suspected of producing the adverse reaction in each subject. Among the possible weaknesses of our study is the time interval between one test and another, during which a spontaneous remission of NSAID hypersensitivity could have occurred. However, remission of NSAID hypersensitivity over time appears to be rare,[17-19] and the different challenge tests in each patient were generally completed in less than 6 months. The use of different NSAIDs and antihistamines adds heterogeneity to the population. Although the use of the same NSAID (eg, aspirin or ibuprofen) in all challenge tests would have produced a greater degree of homogeneity, with this approach there is a risk that the challenge test results will contain "false negatives" if the specific NSAID that the patient had reacted to in the past is not tested. In contrast, if the NSAID that the patient reacted to in the past is used, then the probability of having "true positives" will increase. Regarding the diversity of antihistamines, there were no statistically significant differences between the antihistamines and the results of the challenge tests. So, these results are more likely to be generalizable to clinical practice because they are not limited to a single antihistamine.

CONCLUSIONS

The use of antihistamines can prevent NSAID-exacerbated reactions in patients with CSU who have clinical control over the disease. NSAID challenge tests that use antihistamines allow us to assess tolerance to NSAIDs and remove unnecessary restrictions on patients' NSAID use.

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ONLINE REPOSITORY

TABLE E1. Antihistamines used for CSU and during NSAID challenge test

Antihistamine	Conventional dose	Higher dose
Fexofenadine (n = 28)	15 (53.5)	13 (46.5)
Desloratadine (n = 26)	8 (30.7)	18 (69.3)
Bilastine (n = 20)	12 (60)	8 (40)
Cetirizine (n = 12)	6 (50)	6 (50)
Levocetirizine (n = 8)	6 (75)	2 (25)
Rupatadine (n = 2)	1 (50)	1 (50)

Values are n (%).