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# Nonsteroidal anti-inflammatory drugs hypersensitivity in chronic spontaneous urticaria in the light of its pathogenesis

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## KEY WORDS

*Chronic urticaria; nonsteroidal anti-inflammatory drugs; drug allergy; omalizumab; autoimmunity.*

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## IMPACT STATEMENT

*In chronic urticaria NSAID hypersensitivity is independent on the pathogenesis of the skin disease.*

## Summary

Up to 15% of patients with chronic spontaneous urticaria (CSU) experience severe exacerbations of their baseline cutaneous disease after taking nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase-1 (COX-1) enzyme. These subjects are defined as having a NECD (NSAID-exacerbated cutaneous disease). The way NSAID hypersensitivity correlates with the different pathogenic mechanisms of CSU has not been investigated so far. 235 adults with severe CSU submitted to omalizumab treatment were studied. A rapid omalizumab response was considered as a marker of auto-allergic (Type I) CSU whereas patients showing a slow response or not responding at all were regarded as having a type IIb autoimmune disease. At the first visit medical history of tolerance to aspirin and/or other COX-1 inhibiting NSAID was ascertained. Duration of disease, atopic status, thyroid autoimmunity, CRP, D-dimer plasma levels, and total IgE were assessed appropriately. 23 (10%) were hypersensitive to NSAID. Patients with or without did not differ in any of the variable considered, and a similar proportion in the two groups showed type I or type IIb CSU. The study suggests that in CSU hypersensitivity to NSAID represents a phenomenon that is independent on the pathogenesis of the underlying skin disease.

## Introduction

Chronic spontaneous urticaria (CSU) is a disease characterized by the recurrent occurrence of short-lived wheals with or without angioedema for more than 6 weeks (1). Its prevalence may reach 1% of the general population. Although it may appear at any age, it occurs more frequently in adults, affects more women than men, and may show a familiar pattern (2). In recent years, the pathogenic mechanisms underlying this disease have been partially elucidated, particularly after the introduction of anti-IgE mAb (omalizumab) as treatment. We currently recognize three main subsets of CSU characterized by: a) type I autoimmunity (characterized by an IgE-mediated autoimmune mechanism), b) type IIb autoimmunity (charac-

terized by an IgG-mediated autoimmune mechanism targeting the high affinity IgE receptor or the cell membrane bound IgE itself) or c) hitherto unclear mechanisms. The main markers of the former subset are an elevation of total IgE serum levels and a rapid and frequently complete response to omalizumab. In contrast, patients with type IIb CSU frequently show an association with thyroid autoimmunity (3). Type I and type IIb CSU may overlap in some patients (4). Nonsteroidal anti-inflammatory drugs (NSAID) are the most frequently consumed drugs worldwide, and one of the most frequent causes of drug-induced allergic reactions as well. A large number of studies have eventually led to classify NSAID-induced hypersensitivity reactions into distinct categories (5), one of which specifically addresses the association

of NSAID hypersensitivity with CSU. Patients showing such specific pattern are defined as having NECD (NSAID-exacerbated cutaneous disease); in practice, these CSU patients show a dramatic worsening of the disease after taking NSAID that inhibit Cyclooxygenase 1 (COX-1) enzyme. These subjects generally tolerate selective COX-2 inhibitors (*e.g.*, coxibs or paracetamol). NSAID hypersensitivity may precede by years the onset of frank CSU (6). It has been estimated that up to 30% of CSU patients may have a NECD (7) although this largely depends on the clinical activity of the disease (8). The way NSAID hypersensitivity is associated with CSU in the light of the currently known pathogenic mechanisms has not been investigated so far and represents the issue of the present study.

### Patients and methods

Two-hundred-thirty-five patients (M/F ratio: 75/160; mean age 49.8 years, range 7-89) with severe CSU unresponsive to second-generation antihistamines at any dosage were studied. Following the indications by the Italian regulatory agency (AIFA), omalizumab at a fixed dose of 300 mg/month was prescribed to all patients; the treatment was given for at least three months after which responders could pursue the monthly treatment further, whereas non-responders had to stop it. The reason why the present study included only subjects with severe CSU is that omalizumab response (either rapid/complete or slow/incomplete or absent) represents a good and reliable clinical criterion to discriminate between patients with type I or type IIb autoimmune disease, respec-

tively. Omalizumab response was classified as immediate if UAS7 dropped by at least 80% one month after the first administration, delayed if the clinical response was appreciable within 3 months after the first administration, or absent if no clinical change was appreciable one month after the third administration.

At the first visit, all the participants were thoroughly interviewed about their tolerance to aspirin and/or other COX-1 inhibiting NSAID. Following the current guidelines, patients reporting an unequivocal exacerbation of their disease within two hours after taking at least one COX-1 inhibitor were considered as having a NECD. In most cases, patients showed Emergency Room reports regarding such adverse reactions. All patients with NECD underwent oral challenges with drugs exerting little or no COX-1 inhibition including paracetamol, opiates and coxibs as previously described (9); alternative drugs were tolerated in all cases. Duration of disease was recorded, and all patients were assessed for atopic status by skin testing with a complete panel of commercial extracts of seasonal and perennial aeroallergens (Lofarma, Milan, Italy). Thyroid peroxidase IgG autoantibodies, CRP, D-dimer plasma levels, and total IgE were measured. Patients gave an informed written consent to the use of their clinical data in anonymous form. The Internal review board of the Clinic approved the study. Since the study was observational and based only on routine analyses, a formal approval by an external Ethical Committee was not requested. Means were compared by two-tailed Student's *t* test. Proportions were compared by a  $\chi^2$  test with Yates' correction. Probability values less than 5% were considered statistically significant.

**Table I** - Clinical features of CSU patients with and without NECD.

	Total	NECD	NSAID-tolerant	p
No	235	23	212	
Mean Age	49.8	46.1	50.3	NS
Sex (M/F)	75/160	8/15	67/145	NS
Disease duration (months)	51.8	79.8	48.7	NS
Elevated CRP	41 (17%)	7 (30.4%)	34 (16.0%)	NS
Thyroid autoimmunity	53 (23%)	7 (30.4%)	46 (21.7%)	NS
Elevated D-dimer	94 (40%)	13 (56.5%)	81 (38.2%)	NS
Atopic status	68 (29%)	8 (34.7%)	60 (28.3%)	NS
Elevated IgE	84/180 (47%)	12/17 (70.6%)	72/163 (44.1%)	NS
Early response OMA	162 (69%)	19 (82.6%)	143 (67.4%)	NS
Late response OMA	40 (17%)	4 (17.4%)	36 (16.9%)	NS
No response OMA	34 (14%)	1 (4.3%)	33 (15.6%)	NS

## Results

Results are summarized in **table I**. The study population characteristics were similar to those found in other studies of CSU: about one fourth of patients showed thyroid autoimmunity, and about one third were atopic. D-dimer plasma levels were elevated in 40% of the population, which is not surprising as these were patients with severe CSU. Altogether, based on rapid omalizumab response 69% of patients were considered as having an autoallergic pathogenic mechanism underlying their skin disease. Twenty-three out of 235 (10%) patients had a documented history of severe exacerbations of their underlying cutaneous disease after taking COX-1 inhibiting NSAID. Patients tolerant and not tolerant to COX-1 inhibitors did not show statistical differences in any of the parameters considered, although the latter showed a longer disease duration and a higher prevalence of elevated CRP, thyroid autoimmunity, elevated D-dimer, and elevated total IgE. Similar proportions in the two study groups showed a rapid response, a slow response, or a non-response to omalizumab.

## Discussion

This study group, albeit including only patients with severe CSU, was representative of the general population of subjects with CSU as it showed a prevalence of NSAID hypersensitivity of 10% (8, 10). The recent introduction of the mAb omalizumab for the treatment of recalcitrant CSU led to a tremendous acceleration of our understanding of the etiopathogenesis of this disease. We now know that CSU is in most cases an autoimmune disorder characterized by two distinct mechanisms: one mediated by IgG and one mediated by IgE. Although NSAID hypersensitivity may parallel the activity of the underlying skin disease (8), the present study suggests that it represents an independent event as it occurs equally in rapid, slow, or non-omalizumab responders as well as in patients with elevated or normal IgE levels, with/without thyroid autoimmunity, or with/without atopic diseases. Both NECD and NERD (NSAID-exacerbated respiratory disease) are characterized by specific, similar defects in the metabolism of arachidonic acid (8).

## Conclusions

This study shows that such defects are not associated with a specific pathogenic subset of the underlying skin disorder.

## Fundings

None.

## Conflict of interests

The author declares that he has no conflict of interests.

## References

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, *et al*. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-414. doi: 10.1111/all.13397.
2. Asero R. Chronic idiopathic urticaria: a family study. *Ann Allergy Asthma Immunol*. 2002;89(2):195-6. doi: 10.1016/S1081-1206(10)61937-0.
3. Metz M, Altrichter S, Buttgereit T, Fluhr JW, Fok JS, Hawro T, *et al*. The Diagnostic Workup in Chronic Spontaneous Urticaria-What to Test and Why. *J Allergy Clin Immunol Pract*. 2021;9(6):2274-83. doi: 10.1016/j.jaip.2021.03.049.
4. Asero R, Marzano AV, Ferrucci S, Lorini M, Carbonelli V, Cugno M. Co-occurrence of IgE and IgG autoantibodies in patients with chronic spontaneous urticaria. *Clin Exp Immunol*. 2020;200(3):242-9. doi: 10.1111/cei.13428.
5. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bouchenek G, *et al*. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219-32. doi: 10.1111/all.12260.
6. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. *J Allergy Clin Immunol*. 2003;111(5):1095-8. doi: 10.1067/mai.2003.1444.
7. Blanca-Lopez N, Soriano V, Garcia-Martin E, Canto G, Blanca M. NSAID-induced reactions: classification, prevalence, impact, and management strategies. *J Asthma Allergy*. 2019;12:217-33. doi: 10.2147/JAA.S164806.
8. Doña I, Pérez-Sánchez N, Eguiluz-Gracia I, Muñoz-Cano R, Bartra J, Torres MJ, *et al*. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Allergy*. 2020;75(3):561-575. doi: 10.1111/all.14032.
9. Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Cortellini G, Nizankowska-Mogilnicka E, *et al*. Clinical management of patients with a history of urticaria/angioedema induced by multiple NSAIDs: an expert panel review. *Int Arch Allergy Immunol*. 2013;160(2):126-33. doi: 10.1159/000342424.
10. Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Aspirin-exacerbated cutaneous disease. *Immunol Allergy Clin North Am*. 2013;33(2):251-62. doi: 10.1016/j.iac.2012.10.004.