LETTER TO THE EDITOR

Delayed pressure urticaria affects chronic spontaneous urticaria treatment response: CURE insights

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Key words

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To the Editor,

Some patients with chronic spontaneous urticaria (CSU) have comorbid chronic inducible urticaria (CIndU) (1,2). In a study by Curto-Barredo and colleagues 20% of CSU patients had concomitant CIndU, most commonly symptomatic dermographism (SD; 75%) and delayed pressure urticaria (DPU; 33%) (1). CSU with comorbid CIndU shows long disease duration and has been linked to poor treatment responses to non-sedating antihistamines (nsAHs) (2). It is currently unknown if CSU patients with different comorbid CIndUs differ in their response to high-dose nsAHs. We analysed 412 adult CSU patients enrolled at our UCARE (Urticaria Center of Reference and Excellence), between September 2018 and January 2021, in CURE (Chronic Urticaria Registry), an international academia-driven, open-ended registry for chronic urticaria (https://www.urticaria-registry.com). The inclusion criteria were adult (≥18 years) CU patients. Patients with standalone CIndU were excluded. Patients were assessed by urticaria Activity Score 7 (UAS7), Urticaria Control Test (UCT), and Dermatology Life Quality Index (DLQI) as part of routine clinical practice. All CIndUs were diagnosed by standard provocation testing. In 180 of 412 patients (44%), treatment with a standard-dosed nsAH was not sufficient and escalated to fourfold the standard dose as recommended (3). The efficacy of high dose nsAH therapy was analyzed after 2-4 weeks of treatment. Non-response, was defined as UCT <12 and/or UAS7 >6. Nonparametric statistical methods were used for data analysis in IBM SPSS Statistics V.22. Numeric variables were presented as medians and interquartile ranges (IQRs). Quantitative variables were compared using

Mann-Whitney U test to detect differences between two independent samples and Kruskal-Wallis test to compare multiple unpaired samples. Pearson's chi-squared test was used for qualitative variables. For all tests, a p-value <0.05 was considered statistically significant. The study of the influence of features on predicting response to the respons of high-dose non-sedating antihistamines therapy was performed using a logistic regression model (binary classification). Legitimization with natural (exponential) basis and estimation of 95% confidence interval were applied to the obtained regression equation coefficients. The odds ratio of the predictor of effect on response was visualized in a Forest plot. The ROC-AUC and coefficient of determination (R2) served as a metric of model quality. Of 412 CSU patients, 132 (32%) had one or more comorbid CIndU, most often SD (57%), DPU (24%), cold urticaria (ColdU; 19%), or cholinergic urticaria (CholU; 15%). CSU disease activity (UAS7) and impact (DLQI) were higher, and levels of CSU disease control (UCT) were lower in CSU patients with comorbid DPU as compared to standalone CSU and CSU with comorbid CIndUs other than DPU (all p<0.01; Table I). CSU patients with and without comorbid CIndUs other than DPU showed similar CSU disease activity, impact, and control. Of 412 CSU patients, 180 received high-dose nsAH treatment. The rate of dose escalation was significantly higher in CSU patients with comorbid DPU (20 of 32, 63%) as compared to patients without comorbid CIndUs (118 of 280, 42%, p<0.05) or CSU patients with comorbid CIndUs other than DPU (42 100, 42%; p<0.05). Of the 180 CSU patients treated with a fourfold-dosed nsAH, 120 (67%) were non-responders. The rate of non-response was highest in CSU patients with comorbid DPU (17 of 20, 85%). In contrast, only 26 of 42 patients (62%) with a comorbid CIndU other than DPU and 77 of 118 patients (65%) with standalone CSU who received nsAH-updosing were non-responders. Responders and non-responders did not differ in their gender, age, age at presentation, and urticaria duration. In addition, analysis of response prediction to escalating doses of nsAHs showed that patients with comorbid DPU were less likely to respond to therapy than patients with comorbid ColdU, CholU, or SD. The probability of poor response to therapy was influenced by later disease onset, and positively influenced by male gender, older age, and presence of angioedema (Fig.1). Our findings that many CSU patients with CIndU do not respond to antihistamine treatment including updosing are in line with those of the global prospective AWARE (World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study (4). That CSU is resistant to nsAH treatment in more than half of patients highlights the need for new and better treatment options. The most important result of the present study, i.e. that comorbid DPU adds to the risk of non-response to nsAH updosing, is both expected and surprising. We expected to find that comorbid CIndUs other than DPU also come with increased rates of non-response, but the frequency of comorbid CIndU, overall, in responders and non-responders to nsAH-updosing did not differ in our study. In line with our results, Magen and colleagues previously showed a higher frequency of SD and DPU in patients with nsAH-resistant CSU (2). How comorbid DPU contributes to antihistamine resistance in CSU remains largely unknown. Mast cell mediators other than histamine are held to importantly contribute to the pathogenesis of DPU (5) and may also be drivers of CSU, in patients who have both, CSU and DPU. Patients with CSU should be explored for comorbid DPU, and urther large-scale studies of the effects of comorbid CIndUs on CSU including treatment responses and underlying mechanisms are needed.

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Author Contributions:

DF, EK, MM – the conception and design of the study, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the version to be submitted.

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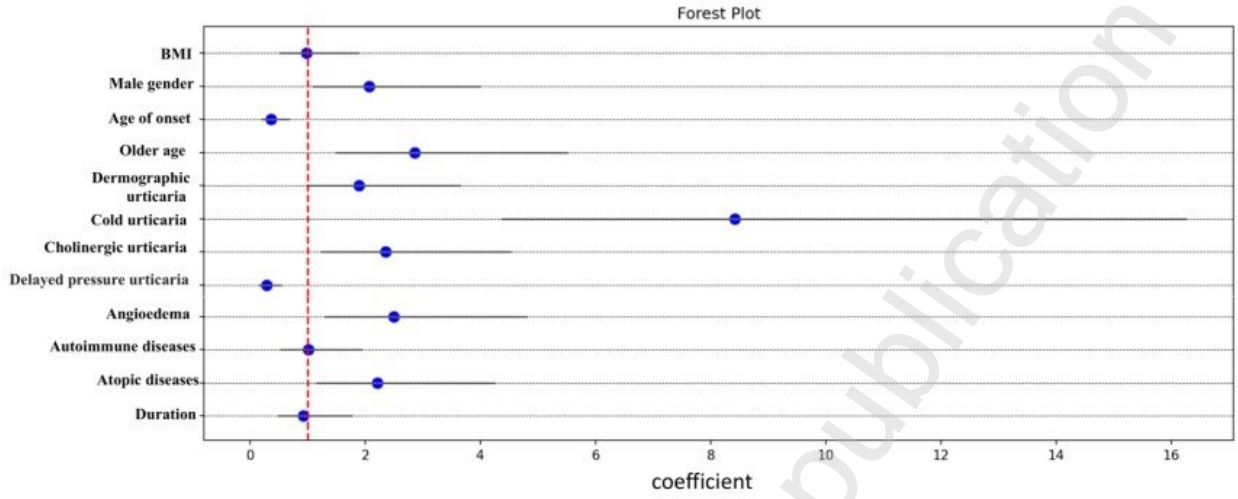
Fig.1 Forest-plot-The influence of features on predicting the response to escalating doses of non-sedating antihistamines



Notes: BMI – body mass index

Table I Comorbid DPU affects CSU response to antihistamine treatment, but other comorbid CIndUs do not

Parameter	Standalone CSU n=280 Group 1	Comorbid DPU n = 32 Group 2	Comorbid CIndU other than DPU n = 100 Group 3	p-value (1vs2)	p-value (1vs3)	p-value (2vs3)
CSU disease activity, impact and control						
UAS7, median (IQR); n	6(0-15), 215	15(7-26,5); 21	6(0-13); 75	0.007	0.679	0.003
DLQI, median (IQR); n	2(1-5), 251	6,5(3-12); 26	3(1-9); 86	<0.001	0.175	0.008
UCT, median (IQR); n	12(8-12), 212	8(5-12); 27	12(9-14); 91	0.008	0.626	0.005
Urticaria treatment						
Standard H_1-antihistamine dose, n (%)	145(52)	10(31)	53(53)	0.018	0.835	0.041
Escalating H_1-antihistamine doses, n (%)	118(42)	20(63)	42(42)	0.019	0.822	0.043

Notes: CSU – chronic spontaneous urticaria; DPU - delayed pressure urticaria; CIndU – chronic inducibel urticaria; UAS7 – Urticaria Activity Score; UCT – Urticaria Control Test; DLQI – Dermatology Life Quality Index; IQR – interquartile range

19 patients had a combination of several CIndU types