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CRP, D-dimer, fibrinogen and ESR as predictive markers of response to standard doses of levocetirizine in patients with chronic spontaneous urticaria

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KEY WORDS

chronic spontaneous urticaria; levocetirizine; ESR; CRP; D-dimer; fibrinogen

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Summary

According to current guidelines, non-sedative H1-antihistamines (nsAH) are the first-line therapy of chronic spontaneous urticaria (CSU). But even up-dosed antihistamines (to four times the standard dose) produce symptom resolution in less than 50% of patients. Biomarkers that can predict the response to nsAH are still unknown. We carried out a prospective study and used discriminant analysis to evaluate the combination of D-dimer, fibrinogen, C-reactive protein and ESR values for predicting the outcome of treatment with levocetirizine in 84 CSU patients. We found that elevation of these parameters is associated with more active disease, low quality of life and lack of response to standard doses of levocetirizine. Thus, evaluation of these markers may be considered useful before starting treatment with nsAH. The mechanisms behind the increase in these parameters in CSU patients need to be elucidated in further studies.

To the Editor

Chronic spontaneous urticaria (CSU) is defined as recurrence of wheals, angioedema, or both for > 6 weeks due to known or unknown causes. According to current guidelines, non-sedative H1-antihistamines (nsAH) are the first-line therapy of CSU (1). But even up-dosing to four times the standard dose can provide symptom control in only less than 50% of CSU patients (2). Identification of biomarkers for predicting the response to nsAH is necessary for developing an individualized treatment. Total IgE, D-dimer, fibrinogen, ESR and C-reactive protein (CRP) have been previously investigated as potential biomarkers of CSU activity and/or response to treatment (3-5). Herein, we for the first time evaluated their combination for predicting the outcome of treatment with levocetirizine in CSU patients.

This prospective study included 84 CSU patients seen from 2012 to 2015 at our Department. Patients with inducible urticaria, urticarial vasculitis and those, receiving anticoagulants, steroids or immunosuppressive agents were excluded. The patients had no history of allergies, thrombosis and chronic infections.

On day 0, all patients stopped taking antihistamines for 5 days. They filled out the Russian versions of Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and Urticaria Activity Score (UAS) on daily basis during this period. On day 5, serum levels of total IgE, D-dimer and fibrinogen were measured using ELISA, CRP - high-sensitive nephelometric method. ESR was determined by Westergren method. Autologous serum skin test (ASST) was performed to assess autoreactivity / autoimmunity. Levocetirizine was then administrated at the dose of 5 mg/day

for 7 days. The efficacy of therapy was evaluated based on CU-Q2oL and UAS scores.

Statistical analysis was performed using SPSS v.22.0 (IBM, New York, USA). Mann-Whitney U-test, Pearson correlation coefficient, chi-square criterion χ^2 and Cramer's V were employed for comparison between the parameters. Discriminant analysis was carried out to reveal predictive markers of response to levocetirizine. We were interested in the relationship between a group of independent variables (ESR, D-dimer, fibrinogen, CRP, total IgE, UAS and CU-Q2oL) and one categorical variable (efficacy of levocetirizine). ESR, D-dimer, fibrinogen, CRP, total IgE values were transformed to normal distribution. A p-value ≤ 0.05 was considered statistically significant.

Of 84 CSU patients (aged 16-77 years), 25 (29.8%) were males and 59 (70.2%) were females. ASST positive patients had significantly more active / severe disease (mean rank: 42.84 vs

31.13, $U = 895$, $p = 0.019$), higher serum levels of CRP (mean rank: 43.02 vs 31.94, $U = 901$, $p = 0.031$) and D-dimer (mean rank: 42.97 vs 30.95, $U = 900.5$, $p = 0.019$) than those with negative ASST.

All patients were divided into two groups based on response to levocetirizine for discriminant analysis: responders ($n = 42$, 50%) and non-responders ($n = 42$, 50%). Levocetirizine was more often effective in patients with mild CSU compared to those with severe disease (66.7 vs 22.9%, $\chi^2 = 3.696$, $p = 0.05$, $V = 0.228$).

Of 42 responders, 7.1%, 9.5%, 12%, 31% and 47.6%, had high serum levels or values of D-dimer, fibrinogen, ESR, CRP and total IgE, respectively. Of 42 non-responders, 54.8%, 26.2%, 35.7%, 54.8% and 23.8% demonstrated elevated D-dimer, fibrinogen, ESR, CRP and total IgE, respectively.

The most important results of discriminant analysis are summarized in **tables 1** and **2**. Mean values of parameters in **table 1**

Table 1 - Discriminant analysis. Distribution of observations into two groups based on efficacy of levocetirizine.

Efficacy of levocetirizine	Parameters	Mean	Standard deviation	Valid N (listwise)	
				Unweighted	Weighted
Effective	ESR	0.7151	0.39204	42	42.000
	D-dimer	2.1248	0.38680	42	42.000
	CRP	0.2859	0.67520	42	42.000
	UAS	3.3810	1.48081	42	42.000
	CU-Q2oL	63.8143	13.22093	42	42.000
	Fibrinogen	0.4647	0.09294	42	42.000
	Total IgE	1.9068	0.75460	42	42.000
Not effective	ESR	1.0797	0.35109	42	42.000
	D-dimer	2.6728	0.47994	42	42.000
	CRP	0.7965	0.58296	42	42.000
	UAS	4.3095	1.48961	42	42.000
	CU-Q2oL	49.8214	15.44157	42	42.000
	Fibrinogen	0.5384	0.13369	42	42.000
	Total IgE	1.5266	0.78568	42	42.000
Total	ESR	0.8974	0.41285	84	84.000
	D-dimer	2.3988	0.51347	84	84.000
	CRP	0.5412	0.67751	84	84.000
	UAS	3.8452	1.54837	84	84.000
	CU-Q2oL	56.8179	15.92696	84	84.000
	Fibrinogen	0.5016	0.12029	84	84.000
	Total IgE	1.7167	0.78918	84	84.000

Table 2 - Discriminant analysis. Within-groups correlation matrix.

Parameters	ESR	D-dimer	CRP	UAS	CU-Q2oL	Fibrinogen	Total IgE
ESR	1.000	0.289	0.410	0.161	-0.140	0.431	-0.034
D-dimer	0.289	1.000	0.440	0.200	-0.318	0.479	-0.153
CRP	0.410	0.440	1.000	0.139	-0.280	0.357	-0.132
UAS	0.161	0.200	0.139	1.000	-0.512	0.089	-0.300
CU-Q2oL	-0.140	-0.318	-0.280	-0.512	1.000	-0.206	0.265
Fibrinogen	0.431	0.479	0.357	0.089	-0.206	1.000	0.120
Total IgE	-0.034	-0.153	-0.132	-0.300	0.265	0.120	1.000

show that responders have higher levels of total IgE and lower levels / values of D-dimer, fibrinogen, CRP and ESR, higher CU-Q2oL and lower UAS scores compared to non-responders. The results of univariate ANOVA's, carried out for each independent variable showed that ESR ($p < 0.001$), D-dimer ($p < 0.001$), CRP ($p < 0.001$), fibrinogen ($p = 0.004$), UAS ($p = 0.005$), CU-Q2oL ($p < 0.001$) and total IgE ($p = 0.026$) significantly differ for responders and non-responders.

Within-groups correlation matrix shows correlations between predictors (**table 2**). There is a positive correlation between D-dimer, fibrinogen, CRP and ESR. As already mentioned, high levels of these are associated with lack of response to levocetirizine (**table 1**). There is also a negative correlation between values of D-dimer and CU-Q2oL, CRP and CU-Q2oL, total IgE and UAS, CU-Q2oL and UAS. Only total IgE correlates positively with CU-Q2oL.

Wilks' lambda is 0.620, ($\chi^2 = 37.471$, $p < 0.001$) indicating a good discriminatory ability of the discriminant function to distribute cases into groups.

The summary of number of subjects classified correctly and incorrectly for responders are 33 (78.6%) and 9 (21.4%), respectively. The summary of number of subjects classified correctly and incorrectly for non-responders are 34 (81%) and 8 (19.0%), respectively. The discriminant function worked equally well for each group of dependent variable. Overall, 79.8% of cases are correctly classified.

To the best of our knowledge, we were the first to assess the set of biomarkers in the same group of CSU patients for predicting response to nsAH. The role of D-dimer and activation of coagulation in CSU pathogenesis is widely discussed (3-5). Patients with high levels of D-dimer, fibrinogen and/or CRP are shown to have severe CSU (3,5,6) that is in the line with the results of our study.

We reported elevation of total IgE serum levels in responders with mild CSU that is contradictory to the findings by Kessel

and co-workers where total IgE was suggested as a marker of severe CSU (7). Thus, the role of total IgE in CSU should be better characterized in further research.

IgG-anti-IgE/FcεRI autoantibodies play a role in a subpopulation of CSU patients (8). We observed that positive ASST is associated with more severe disease, higher serum levels of CRP and D-dimer. Obtained results suggest that positive ASST is more often seen in non-responders.

Thus, we found that the elevation of CRP, ESR, D-dimer and fibrinogen is associated with more active disease, low quality of life and lack of response to standard doses of levocetirizine. Evaluation of these markers may be considered before starting treatment with nsAH. Further research into the mechanisms behind elevation of these parameters in antihistamine-resistant CSU is required.

Learning points

- CRP, ESR, D-dimer and fibrinogen seem to be useful markers for prediction of response to levocetirizine in CSU patients.
- Elevation of these markers is associated with more active disease, low quality of life, and a lack of response to standard doses of levocetirizine.
- Evaluation of these parameters may be considered before starting the treatment with non-sedative antihistamines, and provides additional justification for administration of high doses of antihistamines.

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