

LETTER TO THE EDITOR

A picture of patients with chronic spontaneous urticaria undergoing cyclosporine treatment

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Key words

Chronic urticaria; cyclosporine; omalizumab; IgE; treatment.

To the Editor

Chronic spontaneous urticaria (CSU) is a disease characterized by the recurrent appearance of pruritic wheals with or without angioedema for longer than 6 weeks. In severely affected patients, the disease may not respond to antihistamines, the first line treatment recommended by the international guidelines (1). In these cases, Omalizumab represents the second line therapeutic option along with dupilumab and remibrutinib (1), although the latter two drugs are not yet available for the clinical use in CSU in Europe. The third step of treatment is currently cyclosporine (1-3), a cyclic undecapeptide drug derived from the fungus *Tolypocladium inflatum* that inhibits the calcineurin/NFAT pathway and the JNK and p38 signaling pathways (4). Cyclosporine, which is still widely used as an anti-inflammatory and immunosuppressant agent, has been employed as a long-term treatment for antihistamines-refractory CSU patients well before the appearance of omalizumab (5-7), although its use has been limited by side effects, including hypertension, nephrotoxicity, dyslipidemia, electrolytes alterations, hypertrichosis, higher rates of infection and neoplastic risk, and gingival hyperplasia (8). This study focused specifically on the clinical and serological features of CSU patients who undergo cyclosporine treatment after both antihistamines and omalizumab failure.

Thirty-five patients (M/F 9/26; mean age 50 years, range 16-81) with severe CSU (UAS 7 > 28) unresponsive to both second generation antihistamines at up to 4 times the licensed dosage and omalizumab

(300 mg/month for 4 months, as per the Italian Regulatory Agency, AIFA, prescription) were retrospectively studied. Nonresponse to omalizumab was defined as the absence of any reduction (i.e., >20%) in UAS-7 values from baseline levels 4 months after the start of the treatment. After giving a written informed consent, patients were prescribed oral cyclosporine at a starting dose of 4 mg/Kg/day which was gradually tapered to the minimal effective dosage, up from two weeks after the clinical response to the initial dose, and that was subsequently maintained for at least 3-4 months unless toxicity occurred. Blood pressure and both renal and liver function were controlled at regular intervals to detect signs of toxicity, in which case the drug was stopped immediately. The study population was compared with 269 subjects, also with severe CSU unresponsive to second generation antihistamines at any dosage but responsive, either rapidly or slowly, to omalizumab and that represented the control population. A fast response to omalizumab was defined as the disappearance or a reduction >50% of the UAS-7 score within 4 weeks after the first administration, whereas the response to the drug was defined slow if it occurred within 1 and 3 months after the first administration of the drug. CSU duration (in months) was recorded, and atopic status was ascertained by SPT with a series of both seasonal and perennial airborne allergens who were performed and read following standardized procedures. Plasma D-dimer levels (expressed in ng/mL) were measured by ELISA before the start of omalizumab treatment. Normal D-dimer values were recorded as less than 500 ng/mL. Thyroid IgG autoantibodies, as well as total IgE levels and C-reactive protein were also measured at baseline (EliA anti-TPO and EliA total IgE, Thermo Fisher Scientific, Waltham, MA, USA). Patients were considered as having thyroid autoimmunity in the presence of a positive anti-TPO assay, irrespective of their thyroid functional status. Values > 60 IU/mL were considered positive. The Student's two-sample t-test or the Mann-Whitney non-parametric test was used for the comparisons of continuous variables between groups, as appropriate. The Chi-Square test with Yates' correction was employed to compare the means. Probability values lower than 0.05, two-tailed, were considered statistically significant. The study was approved by the internal review board. Because of its anonymous, and retrospective nature and of the fact it was based on data stemming from routine clinical activity, a formal approval by an external ethics committee was not requested.

All the patients showed a complete (UAS 7 < 6) and rapid (3-10 days) response to the starting dose of cyclosporine. At baseline, patients showed a mean age of 50 years and a M/F ratio of 26/74%. Their

disease duration was 39,6 months (range 2-156 months). CRP scored positive in 10/35 cases (29%). Five out of 35 were atopic (14%), 13/35 (37%) scored positive for IgG-anti TPO autoantibodies, and 17/28 (61%) showed elevated D-dimer plasma levels (range 658-6063 ng/mL). Total IgE levels were measured in 31/35 cases and ranged from 2 to 720 UI/ml (median 13,5 UI/ml). IgE exceeded 40 UI/ml only in 7 patients (20%), and their level was below 20 UI/ml in 19 cases (54%). The comparison with the control population is shown in table 1. Mean age, disease duration, as well as the prevalence of elevated CRP and elevated D-dimer levels did not differ significantly between patients and controls. In contrast, patients showed a significantly higher prevalence of positive TPO autoantibodies, and a significantly lower prevalence of atopic status; both differences were attributable to the early responders control subgroup (table 1). The trends of the study variables in patients and in controls divided by their response to omalizumab are shown in figure 1. The most striking difference regarded total IgE levels which were much lower in patients than both in controls as a whole ($p < 0,001$, table 1) and in both subgroups of controls ($p < 0,001$ and $p < 0,05$ vs controls showing early and late response to omalizumab, respectively). More than 50% of patients showed baseline IgE levels < 20 IU/ml vs only 13% of controls (10% and 23% of early and late omalizumab responders, respectively).

Recently, two mayor endotypes of CSU have been defined, namely type I (also called auto-allergic, which is probably mediated by IgE autoantibodies) and type IIb (autoimmune, which is mediated by IgG autoantibodies directed against the high affinity IgE receptor present on mast cell surface or the surface IgE itself) (9). The two endotypes show specific laboratory features and a different response to omalizumab that is usually rapid in the first subgroup and slow in the second one. The present study evaluated some clinical and serological features of a subset of CSU patients who do not respond at all to omalizumab. Their prevalence (11,5%) was very similar to that of patients that were eventually considered as having a fully autoimmune disease in the PURIST study (10). Interestingly, a continuum trend of some of the clinical/serological variables investigated between rapid, slow and non-responders to omalizumab was observed. Particularly, patients in the cyclosporine group showed IgE levels that were significantly lower than those in both omalizumab responding subgroups, and a higher prevalence of thyroid autoimmunity. Altogether, it is tempting to speculate that, albeit omalizumab slow and non-responders show some common features such as low IgE levels and an elevated prevalence of thyroid autoimmunity (11), they represent distinct populations in which such features are led to the extreme in the latter subset. The slow response to

omalizumab in patients with type IIb CSU has been ascribed to a gradual down-regulation of the high affinity IgE receptors on the mast cells induced by the drug (12). However, the total absence of response to omalizumab that is observed in a minority of CSU patients suggests the possible activity of mechanisms of histamine release that bypass the high affinity IgE receptor in a subset of (type IIb?) CSU patients (13). Altogether, the present study is in line with the data of a previous paper by Kolkhir et al. showing that cyclosporine can be especially effective in selected patients with ai CSU characterized by low total IgE levels and other markers of autoimmunity (14). In conclusion, omalizumab unresponsiveness in CSU is linked in most cases to the lack of circulating IgE, suggesting alternative pathogenic mechanisms for a subset of patients with this disease.

- **Funding:** The study was not funded
- **Conflict of interests:** The author has no conflict of interest to declare

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Table 1: Comparison between patients and controls

	Patients	All controls	Early responders	Late responders
No.	35	269	216	53
M/F	9/26	99/170	82/134	17/36
Mean age (range)	50	52	51	55
Mean DD (months)	39,6	49,1	49,8	46,3
CRP + (%)	10 (29)	48/244 (20)	41/197 (21)	7/47 (15)
TPO IgG + (%)	17/28 (61)	60/244 (25) ***	41/195 (21) ***	20/49 (41)
Atopy + (%)	5 (14)	87 (32) *	75 (35) **	12 (22)
D-dimer + (%)	17/28 (61)	95/220 (43)	74/174 (42)	21/46 (45)
Median IgE (IU/ml)	13,5	118 ***	154 ***	34 *
IgE < 40 IU/ml (%)	80	27	20	53
IgE < 20 IU/ml (%)	54	13	10	23

Statistical significance of the difference with patients: ***= $p < 0,001$; **= $p < 0,01$; * = $p < 0,05$

Figure 1. Some of the study variables in CSU patients undergoing cyclosporine treatment (first column) vs controls responding slowly (second column) or promptly (third column) to omalizumab.

1= Median IgE level (IU/ml); 2=proportion of subjects showing IgE levels < 40 IU/ml; 3= proportion of subjects showing IgE levels < 20 IU/ml; 4= Proportion of subjects showing elevated D-dimer; 5= Proportion of atopic subjects; 6= proportion of subjects showing autoimmune thyroiditis.

