

Letter to the Editor

Plasma D-dimer levels and clinical response to ciclosporin in severe chronic spontaneous urticaria

To the Editor:

Chronic urticaria (CU) is a skin disorder characterized by the continuous or intermittent eruption of short-lived wheals, sometimes associated with angioedema, for more than 6 weeks. Second-generation H1 antihistamines are able to control the disease in most cases, but a significant proportion of patients do not respond, show a heavily impaired quality of life,¹ and pose a challenge for the physician. Severe CU is frequently characterized by an increase in plasmatic markers of thrombin generation and fibrinolysis,²⁻⁴ possibly as a consequence of tissue factor expression by activated eosinophils.^{2,5} The activation of coagulation and fibrinolysis decreases until complete normalization during remission.³ Recent studies found that elevated D-dimer plasma levels might be considered a marker of antihistamine-resistant CU.⁶ Omalizumab proved effective in a large proportion of patients with antihistamine-resistant, severe cases of CU but is still unavailable in many settings including this one, whereas ciclosporin is much more easily available and its efficacy, known for many years, is supported by both case series and controlled trials.⁷⁻⁹ The present study investigated the behavior of D-dimer plasma levels in patients with severe CU undergoing ciclosporin therapy. The study investigated 29 patients (men/women, 9/20; mean age, 46 years; range, 11-75 years) with severe, antihistamine-resistant CU seen during the last 4 years. Patients showed a mean disease duration of 34.0 ± 44.9 months (range, 3-150 months) and a mean urticaria activity score of 4.3 ± 0.5 (range, 4-5). All patients had not responded to different types of second-generation antihistamines given at up to 3× the licensed dose for weeks, and had been treated with short oral prednisone courses as previously reported¹⁰ but relapsed as soon as the doses were tapered down or the drug stopped. In the absence of omalizumab, it was eventually decided to try ciclosporin at a dose of 3 to 5 mg/kg/day (about 4 mg/kg/day in most cases), for a minimum of 3 months, as suggested by previous studies.^{7,8} Plasma D-dimer levels (expressed in ng/mL) were measured by using ELISA before the start of ciclosporin and in 11 cases also during and/or at the end of the treatment. Measurements were carried out in different laboratories scattered throughout this area. Because of the existence of various cutoffs (200, 243, 280, 500, 550, and 570 ng/mL, respectively) as a consequence of differences in standardization between the various producers of the assay kits, plasma levels were “normalized” (proportionally recalculated) to a cutoff of 500 ng/mL to provide a univocal minimum value above which D-dimer levels were considered elevated. Normal D-dimer values were recorded as less than 500 ng/mL, and analyzed as 500 ng/mL in the statistics. Thyroid autoantibodies (TAs), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured at baseline as well. To perform the statistical analyses, the clinical response to ciclosporin (either immediate or in the long term) was arbitrarily assigned a score as follows:

- None: No change in CU severity under ciclosporin treatment (score 0).

- Partial: Some benefit, but pruritus and wheals still present and requiring antihistamine treatment at higher than licensed doses and/or low-dose prednisone (score 1).
- Good: 50% to 80% reduction in pruritus and wheals under antihistamines at licensed dose (score 2).
- Excellent: complete absence of pruritus and wheals taking antihistamines at licensed dose (score 3).
- Remission: complete disappearance of pruritus and wheals without taking antihistamines (score 4).

All clinical investigations were carried out according to the principles of the Declaration of Helsinki; all patients gave their informed consent to both diagnostic and therapeutic procedures. Because the study was based on data stemming from routine clinical activity, approval by an ethics committee was not needed.

Table I presents the clinical features of patients and their response to ciclosporin. TAs were detected in 11 of 28 (39%) patients, and CRP and ESR levels were elevated in 5 of 27 (11%) and 2 of 28 (3%) patients, respectively. Baseline D-dimer plasma levels were elevated in 18 of 29 (62%) patients. Ciclosporin treatment was successful (grade 4 or 3 response) in 17 (59%) patients, partially successful (grade 2 or 1) in 8 (28%) patients, and failed (grade 0) in 4 (14%) patients. In 6 patients, a successful treatment was followed by a relapse after the treatment was stopped. Although in most ciclosporin responders the benefit was rapidly apparent (a marked reduction in the urticaria activity score 3-7 days after starting the drug), in 2 cases the response was eventually good but very slow, appearing only after 1 or 2 months of treatment, respectively. TAs, elevated CRP levels, elevated ESR levels, age, disease duration, and sex were not associated with the clinical response to ciclosporin (scores 0-4) (Mantel-Haenszel test of trend and Kendall rank correlation). In contrast, baseline D-dimer levels showed a highly significant negative correlation with the response to ciclosporin ($\tau = -0.44$; $P < .017$; Kendall rank correlation coefficient assigning a value of 500 to normal D-dimer levels); furthermore, 10 of 11 (91%) patients with normal D-dimer plasma levels versus 7 of 18 (39%) patients with elevated D-dimer plasma levels showed a completely successful response to the treatment (Fisher exact test; $P = .008$). Table II presents D-dimer level trends in 11 patients in whom at least 1 follow-up measurement was performed after starting ciclosporin. In most cases (patient number 2, 4, 10, 14, 21, 24, 27, and 29), D-dimer levels appeared to follow the positive or negative clinical response to the treatment, whereas in other patients (3 and 19) the D-dimer level remained slightly elevated despite an excellent clinical response (Table II). Interestingly, in patient no. 3, D-dimer levels showed a marked tendency to increase when ciclosporin doses were tapered down, possibly suggesting the persistence of the underlying inflammatory process despite the excellent clinical response. In 1 patient, D-dimer levels remained normal throughout the follow-up period.

The activation of coagulation/fibrinolysis parallels disease activity in patients with chronic spontaneous urticaria^{2,4} although whether such activation participates in the pathogenesis of the disease is still unclear. The fact that several previous studies found that anticoagulant therapy (by either oral anticoagulants or

TABLE I. Clinical features of study patients and ciclosporin response

No.	Sex	Age (y)	DD (mo)	UAS	TA	CRP	ESR	Baseline D-dimer level (ng/mL)	Response to ciclosporin	Score
1	M	74	3	4	Neg		Neg	975	Good (80%)	2
2	F	26	50	4	Neg	Neg	Neg	1500	Remission	4
3	F	47	8	5	Neg	Neg	Neg	773	Excellent	3
4	F	60	6	5	Pos	Neg	Neg	692 (1), 970 (2)	Low for 1 mo; good thereafter	1-2
5	M	57	3	4	Pos	Neg	Neg	<500	Excellent but relapse after stopping	4
6	F	18	24	5	Pos	Neg	Neg	583	Remission but relapse after 4 mo	4
7	F	28	10	4	Neg	Neg	Neg	<500	Excellent but relapse after stopping	3
8	F	21	3	5	Neg	Neg	Neg	<500	Remission	4
9	M	75	15	4	Pos	Neg	Neg	<500	Excellent, but relapse after stopping	3
10	F	37	80	4	Neg	Neg	Neg	563	Partial for 6 mo; good thereafter	1-2
11	F	56	4	4	Pos	Pos	Neg	<500	Remission	4
12	F	28	12	4	Neg	Neg	Neg	<500	Remission but relapse after 6 mo	4
13	M	40	5	4	Neg	Neg	Neg	<500	Remission	4
14	F	75	4	4	ND	Neg	Neg	1029	Partial	1
15	F	65	80	4	Neg	Neg	Neg	687	Excellent	3
16	F	27	9	5	Neg	Neg	Neg	1173	Excellent but relapse after 28 mo	3
17	M	70	24	4	Neg	Neg	Neg	<500	Excellent	3
18	M	49	150	4	Neg	Neg	Neg	<500	Excellent	3
19	F	75	3	5	Neg	Pos	Pos	821	Excellent	3
20	F	49	132	4	Pos	Neg	Neg	<500	Excellent	3
21	F	46	6	4	Pos	Pos	Pos	535	Good (80%); partial thereafter	2-1
22	M	59	120	5	Neg	Pos	Neg	551	Remission	4
23	F	31	120	4	Pos	Neg	Neg	1451	None	0
24	F	48	48	4	Pos	Neg	Neg	1137	Good (70%)	2
25	F	55	3	4	Pos	Neg	Neg	<500	None	0
26	F	29	18	4	Neg	Neg	Neg	1628	None	0
27	M	11	3	5	Neg	Pos	Neg	2450	Partial	1
28	F	33	36	5	Pos			2355	None	0
29	M	49	6	5	Neg	Neg	Neg	714	Poor for 2 mo; good thereafter	0-2

Normal values for D-dimer levels are less than 500 ng/mL. Score indicates the category of response to ciclosporin (see text).

DD, Disease duration; ND, not done; Neg, not elevated; Pos, elevated; UAS, urticaria activity score.

TABLE II. Clinical response to ciclosporin in 11 patients followed-up for D-dimer plasma levels

No.	Clinical response to ciclosporin	Months after start of ciclosporin						
		Baseline	1	2	3	4	5	6
2	4 (remission)	1500			<500			
3	3 (excellent)	773	803	732	535	607*	1125*	
4	1-2 (low for 1 mo; good thereafter)	970	525	516	427			
10	1-2 (partial for 6 mo; good thereafter)	563						<500
14	1 (partial)	1029						1830
18	3 (excellent)	<500	<500		<500			
19	3 (excellent)	821	732		696			
21	2-1 (good [80%]; partial thereafter)	535	535	1214	<500			
24	2 (good 70%)	1137		<500		<500	<500	
27	1 (partial)	2450		2350				
29	0-2 (poor for 2 mo, good thereafter)	714	1241		<500		517	

*Ciclosporin dose being tapered down.

heparin) is extremely effective in some cases seems to support a pathogenic role, at least in selected patients. In the present study, baseline D-dimer plasma levels were elevated in more than 60% of the patients; this observation is not surprising because the patients studied here represented a minority of subjects with CU with a particularly severe disease, unresponsive to standard treatments. Nonetheless, D-dimer levels followed the clinical response to ciclosporin treatment in most of the followed-up patients. The rate of clinical response to ciclosporin treatment was extremely good, similar to that observed in

previous studies (7-9). Altogether, although the data used in the present study stem from routine clinical care and lack the rigor associated with a clinical research study, these observations confirm that D-dimer is a good marker of disease activity in most patients with spontaneous CU, and show that such parameter may also be useful to monitor the clinical response to ciclosporin treatment in most patients with severe disease.

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