

Serial D-dimer plasma levels in a patient with chronic spontaneous urticaria developing resistance to omalizumab

R. Asero¹

¹Allergy Department, Clinica San Carlo, Paderno Dugnano (MI), Milan, Italy

doi:10.1111/ced.13181

Summary

Chronic spontaneous urticaria (CSU) is a condition presenting as the spontaneous occurrence of itchy wheals with or without angio-oedema for > 6 weeks. A patient with severe chronic spontaneous urticaria who developed resistance to omalizumab is described. The patient's D-dimer plasma levels strictly paralleled the disease activity despite the administration of anti-IgE therapy.

Chronic spontaneous urticaria (CSU), defined as the spontaneous occurrence of itchy wheals with or without angio-oedema for > 6 weeks, is a rather frequent disorder that may greatly hamper quality of life for patients, particularly when it occurs in a severe, anti-histamine-resistant form. Previous studies have shown that severe CSU is frequently associated with increased D-dimer plasma levels caused by the activation of the extrinsic pathway of the coagulation cascade, and that D-dimer levels normalize when the disease goes into remission.¹ Further, elevated D-dimer levels are associated with resistance of the disease to antihistamine therapy.² Three double-blind, placebo-controlled, phase 3 studies have clearly shown that omalizumab is highly effective in patients with severe, unremitting urticaria that does not respond to second-generation antihistamines at higher than licensed doses.³ The recently revised European Academy of Allergy and Clinical Immunology guidelines for the treatment of CSU place ciclosporin and omalizumab at the same step of treatment; however, omalizumab is far less toxic and hence preferable over ciclosporin as a first therapeutic option in antihistamine-resistant patients, despite its higher cost.

This report details a patient with severe CSU, who had only a temporary response to omalizumab and

whose D-dimer plasma levels were serially measured during the different phases of the disease.

Report

A 47-year-old woman presented with a 3-month history of severe generalized urticaria with recurrent angio-oedema unresponsive to antihistamine treatment (cetirizine) even at higher than licensed doses (up to 40 mg/day) and only partially and temporarily responding to oral prednisone 25 mg/day per 5 days. The patient had a selective IgA deficiency, and baseline *in vitro* investigations revealed that thyroid autoantibodies (both anti-thyroglobulin and anti-thyroperoxidase) were positive, and D-dimer plasma levels were elevated (3929 ng/mL; normal < 500 ng/mL), whereas full blood counts, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies and complement fractions were normal. The patient reported a slight, inconsistent elevation of thyroid-stimulating hormone levels, but other thyroid hormone levels were always normal. A weekly Urticaria Activity Score (UAS-7) of 38 was calculated from clinical recordings.

Subcutaneous omalizumab 300 mg/month was started as an add-on treatment to a licensed dose of cetirizine, and 3 days after the first administration, the patient reported a dramatic improvement that was quantified as 98% on a visual analogue scale (corresponding to a UAS-7 of 2). Two weeks after the first administration of the drug, the patient's D-dimer levels had dropped to 785 ng/mL. The disappearance of the CSU persisted after the second dose; 2 weeks after the

Correspondence: Dr Ricardo Asero, Ambulatorio di Allergologia, Clinica San Carlo, Via Ospedale 21, 20037 Paderno Dugnano (MI), Milan, Italy
E-mail: r.asero@libero.it

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 27 November 2016

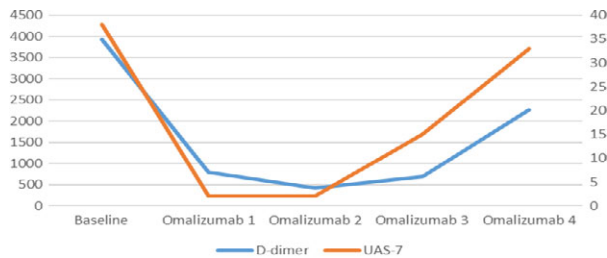


Figure 1 Weekly Urticaria Activity Score (UAS-7) and D-dimer plasma levels at baseline and during omalizumab treatment in a patient with chronic spontaneous urticaria.

administration of the second dose of omalizumab, D-dimer plasma levels had decreased further to 419 ng/mL. Four weeks after the third omalizumab dose administration, the patient reported a relapse of the skin weals, sometimes associated with angio-oedema of her face. At this point, D-dimer plasma levels were 688 ng/mL. The clinical worsening continued after the fourth dose of omalizumab, and was associated with an increase in D-dimer levels up to 2269 ng/mL and a UAS-7 of 33. The disease severity and D-dimer plasma levels are summarized in Fig. 1. At this point omalizumab was stopped, and ciclosporin 4 mg/kg day was prescribed. The effect of this treatment could not be assessed because the patient moved away and was lost to follow-up.

The pathogenesis of CSU is still debated, but it is generally accepted that its origin is probably autoimmune in a proportion of cases, and is due to the presence of functionally active IgG autoantibodies specific for the high-affinity IgE receptor on mast cells and basophils, FcεRI, or for IgE.⁴ The presence of both thyroid autoantibodies and selective IgA deficiency, a condition that is frequently associated with autoimmune disorders, indirectly suggest that our patient probably had an autoimmune CSU. The patient had very severe urticaria and showed an excellent initial response to omalizumab, with virtually complete disappearance of the angio-oedema, weals and pruritus but, unexpectedly, the effect vanished after 3 months of treatment.

The mechanism of action of omalizumab in CSU is still unknown, but it has been suggested that its efficacy relies on the downregulation of the high-affinity IgE receptor on mast cells and basophils, eventually leading to reduced activation of these cells.⁵ However, such effects require 3–4 weeks to occur, whereas the clinical benefit is often visible after as little as a few days. However, omalizumab has been reported to exert a number of other effects at

different levels,⁶ including the coagulation cascade, eventually resulting in a reduction in D-dimer plasma levels.⁷

Development of resistance to omalizumab in a patients previously responding to the drug has been reported previously,^{8,9} but the reasons for this are unclear. One possible explanation is that the pathomechanisms leading to histamine release in CSU are many, and that their relative importance may vary from one patient to another or may change over time in the same patient. Omalizumab would be able to interfere only with some, and not all of these. Another interesting aspect of this case of CSU is that the patient's D-dimer levels strictly paralleled the severity of the disease during both the phase of response to omalizumab and the subsequent phase of omalizumab resistance. This suggests that the reported effects of omalizumab on D-dimer⁷ levels might not be directly caused by the drug but could simply reflect the reduction of the general inflammatory state that accompanies the remission phases of the disease. Antifibrinolytics such as tranexamic acid have been shown to be effective in some patients with CSU with elevated D-dimer levels; however, the proportion of patients responding to this drug is limited, and the therapeutic guidelines do not recommend its use on a routine basis.

In conclusion, this was an unusual case of CSU with initial response to omalizumab, but later recurrence while still under treatment. This clinical case confirms that D-dimer is an excellent marker of disease activity in a subset of patients with CSU.^{1,10}

Learning points

- Resistance to omalizumab may develop in patients with CSU.
- D-dimer strictly parallels disease activity in a subset of patients with CSU.
- The drop in D-dimer levels induced by omalizumab in patients with CSU might not be due by a direct effect of the drug on the coagulation cascade but might rather reflect the reduction of the inflammatory state that characterizes the disease.

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