

Baseline D-dimer plasma levels correlate with disease activity but not with the response to omalizumab in chronic spontaneous urticaria

To the Editor

Studies carried out during the last decade have largely demonstrated that an activation of the coagulation cascade may be observed in patients with severe chronic spontaneous urticaria (CSU).¹⁻³ Such activation occurs mostly via the extrinsic pathway and strictly parallels the activity of the disease. Activated eosinophils, hyper-expressing tissue factor, seem the main initiators of these phenomena,⁴ although endothelial cells may concur as well.⁵ The potential relevance of thrombin as well as of other activated coagulation factors in amplifying the release of histamine from mast cells and basophils, thus worsening the disease status, is suggested by several studies reporting the efficacy of anticoagulants in patients with severe CSU not responding to antihistamines at any dosage.³

The humanized anti-IgE mAb, omalizumab, has become a mainstay of the treatment of severe CSU during the last years. Patients' response to this biological may be very rapid (as short as a few days after the first administration), slow (requiring 3-4 month of therapy), or absent in a minority of patients. Such different pattern of response to omalizumab has prompted possible differences in the pathogenesis of the disease; in effect, recent studies demonstrated the presence of circulating IgE autoantibodies in patients who show a prompt response to the drug, whereas late and nonresponders probably represent a subset characterized by an IgG-mediated autoimmune mechanism directed to the high-affinity IgE receptor of to IgE.^{6,7}

Although some recent studies found that the levels of the fibrin fragment D-dimer, a biomarker of coagulation activation, parallel the response to omalizumab in patients with CSU,⁸ the way these two variables are interconnected each other has not been studied in detail so far. We investigated this aspect in the present study.

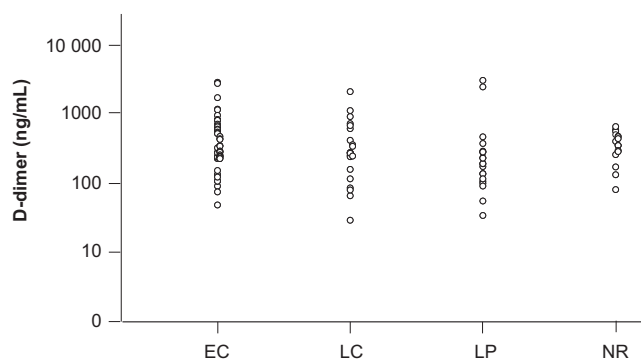


FIGURE 1 D-dimer plasma levels in patients showing a different pattern of response to omalizumab. EC, early complete; LC, late complete; LP, late partial; NR, no response

One hundred sixty-one adult patients (M/F 43/118; mean age 48 ± 16 years, range 15-80 years) with both active and severe CSU (baseline UAS-7 > 20) not responding to second-generation antihistamines at doses up to 4 times higher than the licensed dose and submitted to subcutaneous omalizumab treatment at a dose of 300 mg/month for at least 3 months were studied. Baseline D-dimer plasma levels were measured by ELISA in order to assess the correlation of this biomarker with the disease activity and the response to the drug; levels exceeding 50 ng/mL were considered positive. The clinical response to omalizumab was assessed by UAS-7 recordings and classified as early if it occurred within 4 weeks after the first administration, late (if the response could be observed within 3 months), or absent (no detectable response 1 month after the third administration). The clinical response was defined as complete if UAS-7 showed a reduction of 90% or more, partial if the reduction ranged between 50% and 90%, or absent in the presence of variations < 50% of UAS.

Ninety patients (55.9%) showed an early and complete response to omalizumab; their mean baseline D-dimer level was 1186 ± 1199 ng/mL. Twenty-eight patients (17.4%) had a late and complete response; their mean baseline D-dimer level was 892 ± 1045 ng/mL; 20 patients (12.4%) showed a late and partial response and a mean baseline D-dimer level of 988 ± 1762 ng/mL, while 23 patients (14.3%) did not respond to the drug (baseline D-dimer 826 ± 973 ng/mL) (Figure 1). A significant correlation between D-dimer and UAS-7 at baseline was found ($P = 0.014$; Figure 2), whereas D-dimer levels used as a marker of the activation of the

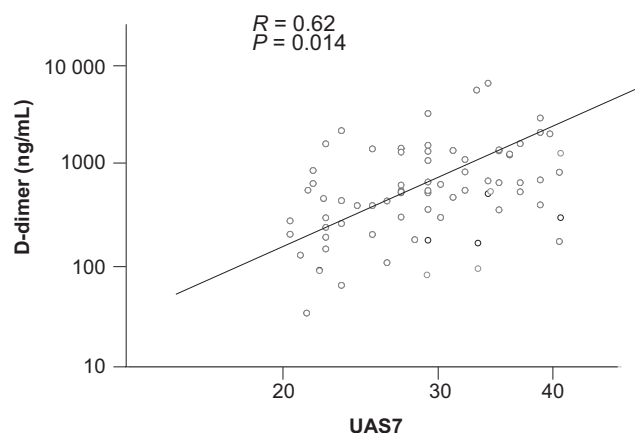


FIGURE 2 D-dimer plasma levels as a function of urticaria activity expressed as UAS-7 score

coagulation cascade and of its intensity were not able to predict the clinical response to omalizumab.

Our data confirm that the activation of the coagulation cascade represents a marker of CSU severity,¹ as it does not occur in subjects with a mild disease. The lack of an association between baseline plasma D-dimer levels and response to omalizumab suggests that the activation of the coagulation cascade, starting with the hyper-expression of tissue factor by eosinophils and endothelial cells triggering the extrinsic pathway, does not depend on a specific pathogenic mechanisms underlying CSU (such as IgE-mediated autoimmunity, IgG-mediated autoimmunity, or other hitherto unknown mechanisms⁹) but rather represents a relevant nonspecific amplification mechanism in a subset of severely affected patients. The reasons why the coagulation cascade is not activated in all patients with severe CSU need to be elucidated.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Efficacy of mepolizumab in patients with previous omalizumab treatment failure: Real-life observation

To the Editor,

Asthma is a common chronic disease, usually characterized by reversible airflow obstruction and airway inflammation, with a worldwide prevalence of more than 315 million patients, with about 10% of them having a severe or uncontrolled form.¹ Usually, asthma symptoms can be controlled by inhaled corticosteroids, with or without long-acting β_2 -agonist. Other drugs can be added to improve the

control, such as long-acting antimuscarinic agents, antileukotrienes, or immunotherapy.²

Uncontrolled patients continue to exacerbate and often need oral corticosteroids (OCS), even in prolonged courses. Several biological drugs were introduced for severe asthma, with the aim of reducing exacerbations and the need for OCS.³ The first one, commercialized about 15 years ago, was the anti-IgE omalizumab (OMA),