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Case Report

Differences in Basophil Activation along Treatment with Antihistamines and Omalizumab in Chronic Spontaneous Urticaria

Ana Rodríguez Trabado[1*], Carmen Cámara Hijón[2], Luis Miguel Fernández Pereira[2]

[1]Allergy Department, Nuestra Señora del Prado Hospital, Talavera de La Reina (Toledo), Spain

[2]Immunology Department, San Pedro de Alcántara Hospital, Avda. Pablo Naranjo S/N, 10002 Cáceres, Spain

[*]**Corresponding author:** Ana Rodríguez Trabado. Allergy Department, Nuestra Señora del Prado Hospital, Talavera de La Reina (Toledo), Spain. Tel: +34 925 80 36 00; Fax: +34 925 81 54 44; Email: trabadoro@yahoo.es

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Abstract

The serum of patients with Chronic Spontaneous Urticaria (CSU) is able to induce activation of basophils of healthy donors, assessed by Basophil Activation Test (BAT). In three patients treated with antihistamines the BAT persisted as positive along the treatment, whereas patients treated with omalizumab experienced an early and maintained decrease of basophil activation.

Introduction

The mechanisms causing Chronic Spontaneous Urticaria (CSU) cannot be clarified in a high percentage of cases. But in up to half of them an autoimmune mechanism is responsible, trough IgG auto antibodies against the high-affinity IgE receptor (FceRI) or even against IgE [1,2]. This finding allowed the indication of the treatment with omalizumab in CSU, due to its capacity of down-regulate the high-affinity IgE receptor expression, and then the immune response. These antibodies, also present in a low proportion of healthy people, are functional only in patients affected by CSU, as in whom they are able to release histamine [3]. Other elements, not so well studied, can activate basophils in this pathology, such as coagulation factors [4,5], complement and cytokines [6], suggesting other mechanisms different than the autoimmune.

In the cases with an underlying autoimmune mechanism, several tests can be performed. The most commonly used are the autologous Serum Skin Testing (ASST) and the Basophil Activation Test (BAT), although the factors implicated in degranulation are not still enough clarified. The first is the intradermal injection of serum of a CSU patient in the volar aspect of the forearm [7]. The BAT is performed taking in account that the serum of CSU patients is able to induce activation of basophils of healthy donors, which can be evidenced by the expression of the activation markers, CD63 [8,9] or CD203c [10]. The ASST has a sensitivity around 43.4-45.5%, but there are also positive results in healthy individuals [11]. The BAT sensitivity varies from 30% to 40% if the activation is assessed trough 203c [10]; and up to 68% using CD639. The BAT offers many advantages in comparison with ASST. Its specificity and reproducibility are better [9], it has easier interpretation, is not interfered by the antihistamines intake, there is no risk of biological accidents for the patient and the assay can be performed with serum of many controls in order to assess the result. The kinetics of histamine liberation seem to be the same in basophis and mast cells [12] and parallel to the expression of CD63 [13], so the BAT could be used as a reference to study the CSU.

Although the pathogenic study in CSU is not routinely performed and the diagnosis and management of affected patients should still be driven according to a clinical approximation, an autoimmune study can be of high interest. A positive result has been associated with a major severity and duration of the disease [14] and can be useful in the differential diagnosis when the clinical picture is not enough clear. It has also been useful in monitoring the evolution of patients treated with biological agents [15]. The therapeutic steps are established by the clinical guidelines according to the severity of the disease, in order to achieve a symptomatic control [11,16]. Nevertheless, when the pathogenic mechanism can be assessed, the monitorization of patients following different treatments could help to investigate the differences among them in achieving the control of the disease.

Patients and Methods

Eight patients affected of CSU were monitored along their treatment by way of basophil activation test. Seven patients were female and one male, with ages comprised between 56 and 18 years. Five of them followed treatment with omalizumab 300 mg per month. The other three were treated with antihistamines (rupatadine 10 mg and ebastine 20 mg, twice and once a day, respectively). Two of the patients treated with omalizumab were also in treatment with low dose of prednisone (10 mg/ day) and antihistamines twice a day, in spite of which they required one to three cycles of prednisone (0.5-1 mg/kg/day) per month due to exacerbations. The other two patients required equally short cycles of oral steroids every month. The BAT was performed basally, at the diagnosis, and along the treatment with both drugs. No oral corticosteroids at medium or high dose were allowed the three previous weeks to performing the test.

In patients treated with omalizumab, each assay was performed one month after receiving the last dose. The first case was studied along a year of treatment with omalizumab. The test was performed at the diagnosis and one, two, six and twelve months after beginning the treatment. The other four cases were studied until obtaining maintained significant changes in basophil activation. In patients treated with antihistamines, an initial test was performed and a second elapsed eighteen months. The last case concerns a female patient with severe asthma treated with omalizumab 150 mg that developed CSU along the treatment. As the clinical control with antihistamines was optimal, the omalizumab dose was not duplicated, so she was considered as a case treated with antihistamines. The BAT was performed according to the protocol previously described [15]. The percentage of basophils expressing CD63 with affinity was the variable used to determine basophil activation. Briefly, a heparinized whole blood sample was drawn from the donors and aliquot to test several stimulus (the CSU patients serum and the negative and positive controls). The analysis was performed within 24 hours after the extraction. A stimulation buffer containing IL-3 at 10 ng/ml was first added for ten minutes.

Each sample was tested with a negative control (serum saline), (Figure 1b), showing the basally activated basophils, before adding any stimulus; a positive control with anti-IgE, (Beckman Coulter, Spain) (Figure 1c), that induces basophil activation; and the serum of the CSU patients (Figure 1d-i). Each serum was tested in three healthy donors. A double binding was carried out with CD203-PE, to select the basophil population, and CD63-FITC, to detect its activation (Figure 1). After a lysing and washing process, the analysis was performed by flow cytometry (Flow cytometer FC500, Beckman Coulter, software MXP y Kaluza). The acquisition included almost 500 basophils. The analysis gate was defined around cells showing high-density CD203c label and low side-scatter, identified as basophils (Figure 1a). The test was considered positive if at least 15% of basophils became activated after adding the CSU serum (after subtracting the negative control) [8,9]. Ten control assays were performed testing the serum of individuals without CSU and five with sera of patients affected by other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. ASST was also basally performed to complete the autoimmune origin of the disease.

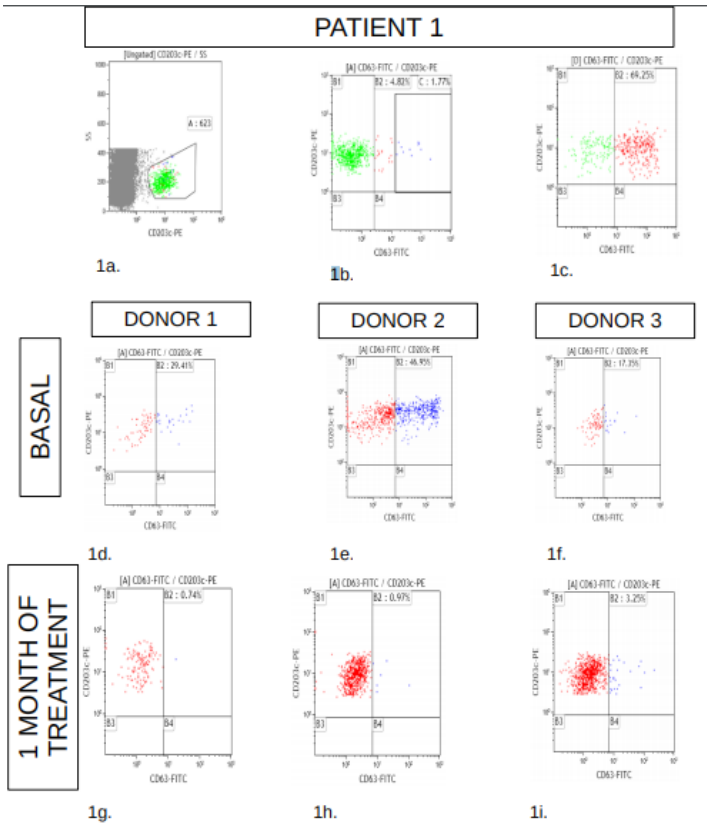

Figure 1: Monitorization of basophil activation after one month of treatment with omalizumab in patient 1.**(1a)** basophil population of patient 1; **(1b)** negative control; **(1c)** positive control; **(1d-f)** basophil activation in individual controls 1, 2 and 3 after adding the serum of patient 1; **(1g-i)**, basophil activation in individual controls 1, 2 and 3 after adding the serum of patient 1 one month after receiving the first dose of treatment.

Results

The ASST was positive in the three patients treated with antihistamines and in three of the five patients treated with omalizumab, although two of the positive patients were even under treatment with oral steroids at low dose when it was performed. No positive BAT results were obtained testing the sera of controls, including those belonging to patients with autoimmune diseases. In the first case treated with omalizumab, before beginning the treatment an activation even higher than that induced by the

positive control was seen in donors (Figures 1d-f and Figure 2). Already after one dose of treatment, the activation induced by the serum patient decreased to values similar to the negative control (Figure 1g-i and figure 2). This decline was consistent with a significant clinical improvement. No new cycles of oral steroids were required and the antihistamines were stopped three days after receiving the first dose of Omalizumab. This change was maintained after two, six and twelve doses of treatment. In other two cases treated with omalizumab a test negativization was observed after the first month of treatment (Figure 2). None of them needed new cycles of oral steroids, that they previously took one or three times a month, and the patient that followed chronical intake of prednisone could stop it.

In the other two remaining patients following omalizumab, after two months of treatment a BAT negativization was observed (Figure 2). One of them still required oral steroids during the three days after receiving the first dose of Omalizumab, achieving afterwards a good control with antihistamines (bilastine 20 mg). The last patient could stop the chronic intake of prednisone 10 mg after the first dose, and only presented sporadic lesions with the intake of antihistamines (40 mg of bilastine per day). In the subgroup of patients only treated with antihistamines (Figure 2), in patient 6 the test performed after eighteen months resulted negative, coinciding with a spontaneous resolution of the disease. In patient 7, the second test performed was positive, with activation values similar to the initial ones, consistent with a persistent activity of the disease. And finally, in the patient that developed urticaria in spite of the treatment with Omalizumab 150 due to bronchial asthma, the test persisted as positive after twelve and eighteen months of treatment, according to the need of chronic intake of antihistamines to control de disease.

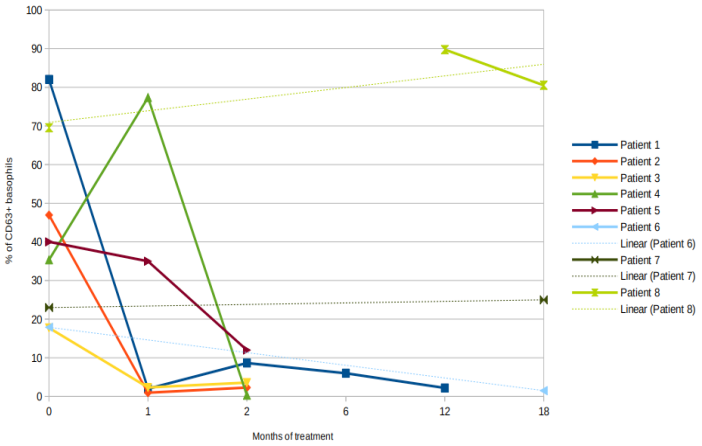

Figure 2: Basophil activation along the treatment. Changes in basophil activation along the treatment with omalizumab and antihistamines. A tendency line is showed for patients with no more than three determinations (patients treated with antihistamines).

Discussion

Chronic spontaneous urticaria is a disease with a high impact in patients' quality of life. Up until not so many years ago, only treatments with antihistamines and immunosuppressive drugs were available. The knowledge of new physio-pathological mechanisms implicated in the disease, such as the autoimmune, allowed the indication of treatments with less side effects, like omalizumab. Nevertheless, the pharmacological mechanisms of this drug in the disease are not completely known, and it is suspected than they go far than the down-regulation of the expression of the high-affinity IgE receptor. Then, the study of the cellular response with different treatments could help to improve the management of the disease. In these cases of CSU, where an autoimmune mechanism is suspected, the BAT was useful to monitor and to compare the therapeutical effect of the different drugs.

Previous works propose that the kinetics of expression of the basophil activation marker CD63 is parallel to that of the histamine liberation [12,17], making possible to monitor the disease trough BAT. In comparison with ASST, the BAT is more adequate to this proposal. The results of the first can be influenced by the antihistamines intake and by a cellular energy after recent lessons or demographic phenomena. So, a hypothetical variation of the papule size along the disease would not be feasible. Whereas, the numeric result of BAT, given as percentage of activated basophils after analyzing minimum of 500 cells, can clearer show significant changes after a treatment, as it has been shown in patients treated with venom immunotherapy [18]. This study shows differences in the therapeutical effect of antihistamines and omalizumab. Whereas in patients treated with antihistamines the test persisted as positive, patients treated with omalizumab experienced an early decrease of basophil activation. Omalizumab tends to be considered only as a symptomatic treatment more potent than antihistamines, then used as a second line.

Far from this, this finding could shows an immunomodulatory effect of omalizumab, absent in patients treated with antihistamines, in whom only a symptomatic control seems to be evident. In respiratory allergy is in discussion the immunomodulatory effect of omalizumab. Whereas it was initially considered also as a symptomatic treatment, studies show persistence of clinical improvement and immunological changes after finishing the treatment [19]. In the case of CSU, the therapeutical mechanism based on a down-regulation of the IgE receptor in the surface of cells implicated in chronic urticaria could be related with immunological changes [20]. It also would be of interest to relate the mentioned findings with the time resolution of the disease, recurrences, the duration of free symptoms periods or even to apply them in the evaluation of the efficiency of the dose reduction or spacing in patients treated with Omalizumab.

Conclusion

The basophil activation test could help to evaluate the different therapeutical effects of the drugs used in chronic spontaneous urticaria.

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