Omalizumab is effective in patients with chronic spontaneous urticaria plus multiple chronic inducible urticaria

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Chronic urticaria (CU) is characterized by wheals and/or angioedema for more than 6 weeks, with a point prevalence of 0.1-1.4% (1, 2). CU is classified as chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), which can occur simultaneously or independently (3). In CSU patients, concomitant CIndU has been associated with severe, long-lasting and/or antihistamine-resistant CSU (4). Omalizumab, an anti-IgE monoclonal antibody, can improve both CSU and CIndU in the same patients (5, 6). However, its efficacy in CSU patients with several subtypes of CIndU is poorly characterized (6, 7). Here, we describe six patients with antihistamine-resistant CSU and multiple CIndUs (Table 1) treated with 300 mg omalizumab monthly and followed up for a period of 3-11 months.

Common blood count and serum levels of total IgE, C-reactive protein (CRP), eosinophil cationic protein (ECP), D-dimer and fibrinogen were measured at baseline and 30 days after the injection of omalizumab. The Urticaria Activity Score (UAS) was obtained for 30 days (before and during the treatment). Dermatology Life Quality Index (DLQI) was used at baseline and every 7 days. The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and the Urticaria Control Test (UCT) were applied at baseline and 30 days after the first omalizumab injection. Provocation tests with appropriate triggers were performed according to the international guideline (1).

The age of patients ranged from 26 to 52 years (mean: 43 years, Table 1). The mean duration of CSU and CIndU was two and three years, respectively. In three cases, CIndU appeared before CSU, and in the other three patients CIndU developed after or at the same time as CSU. Provocation tests were positive before treatment in all patients. Concomitant symptomatic dermographism (SD), delayed pressure urticaria (DPU) and cholinergic urticaria were diagnosed in six, four, and four patients, respectively. Two and four CSU patients had two and three different subtypes of
ClnDU, respectively. All patients had wheals and three of them experienced several episodes of angioedema. All patients had uncontrolled disease.

In all patients, disease control was reached, and quality of life was improved within one month after the first omalizumab injection (Table 1). Provocation tests became negative in four patients. In two patients with SD or DPU, provocation tests remained slightly positive, but everyday ClnDU symptoms were gone.

Partial improvement assessed by UAS7 was seen in all patients after the first injection and five of six patients reported complete remission of their CSU after the second injection. Four patients were fast responders and two were slow responders as assessed by UAS and UCT scores (Table 1). In five patients, the symptoms of CSU and ClnDU decreased at the same time. In two slow responders, ClnDU symptoms disappeared 2-3 weeks before improvement of CSU symptoms (Figure 1a-d).

In all patients, total IgE levels were elevated after the treatment as compared with their baseline values (Table 1) as described before (8). In the literature, low levels of total IgE at the baseline have been reported to be associated with nonresponse and/or slow response to omalizumab (9). However, we did not observe this in all patients probably because of the small number of patients included.

Similarly, decrease in CRP and D-dimer levels after successful treatment with omalizumab has been reported (8). In our patients, no difference was seen in levels of ECP, D-dimer, CRP and fibrinogen before and after treatment. In two patients, elevated D-dimer levels were present before the onset of their urticaria and might be associated with concomitant diseases.
The pathomechanism of chronic urticaria is yet to be clearly defined. It is still unknown what causes this activation and degranulation of tissue-resident mast cells and the subsequent release of inflammatory mediators. Type I autoimmunity ("autoallergy") is thought to be a cause of both CIndU and CSU in a subpopulation of patients. Autoallergic urticaria is characterized by the synthesis of autoantigen (autoallergen), which is detected by specific IgE autoantibodies bound to skin mast cells that results in degranulation of mast cells. For example, some IgE autoantibodies have been described in CSU, namely IgE against thyroid peroxidase, interleukin-24 and tissue factor. In patients with Type I urticaria, omalizumab can prevent binding of IgE to the high-affinity IgE receptor and, therefore, suppress mast cell activation and release of histamine and other mediators. However, some CSU patients respond more slowly to omalizumab that is consistent with Type IIb autoimmunity associated with IgG autoantibodies against IgE and FcεRI. In these patients, treatment with omalizumab can result in the loss of membrane-bound IgE and subsequently FcεRI from skin mast cells that prevents the activation of mast cells by IgG autoantibodies (1, 5, 10, 11).

In line with other publications (5, 6, 10-12), our patients with CSU plus several subtypes of CIndU responded well to omalizumab treatment, which resulted in decreased urticaria activity, provocation test responses and increased quality of life and disease control. Prospective treatment studies with omalizumab, in patients with CIndU with and without CSU, children and adults, should be performed.

**Disclosure of potential conflict of interest:**

Pavel Kolkhir is a speaker for Novartis and Roche.

Anastasiia Allenova is a speaker for Novartis.
Dayana Skander has no conflict of interest.

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Table 1. Demographic characteristics of patients

<table>
<thead>
<tr>
<th>#</th>
<th>Sex</th>
<th>Age, years</th>
<th>Duration of CSU / CIndU, years</th>
<th>Type of CIndU</th>
<th>Before / 4 weeks after the first omalizumab injection</th>
<th>Response to omalizumab (UAS7), after 1st / 2nd injection</th>
<th>Speed of response***</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>27</td>
<td>3/3</td>
<td>SD, DPU, LHU</td>
<td>No/No</td>
<td>50/195</td>
<td>Fast</td>
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<td></td>
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<td>Pattern/Complete</td>
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<td></td>
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<tr>
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<td>26</td>
<td>6/5</td>
<td>CHU, ColU, SD</td>
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<td>Partial/Complete</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All CIndUs e/-</td>
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<td>Fast</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>31</td>
<td>1/2</td>
<td>CHU, SD, DPU</td>
<td>No/No</td>
<td>8/54</td>
<td>Partial/Complete****</td>
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<td></td>
<td></td>
<td>Pattern/Complete</td>
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<td>Fast</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>26</td>
<td>1/1</td>
<td>SD, DPU</td>
<td>No/No</td>
<td>15/87</td>
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<td>45</td>
<td>2/3</td>
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<td>Yes/No</td>
<td>15/87</td>
<td>Partial/Complete****</td>
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<td>Pattern/Complete</td>
<td>652/645</td>
<td>Slow</td>
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</table>

UCT: Urticaria Control Test; DLQI: Dermatology Quality of Life Index; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; CIndU: chronic inducible urticaria; F: female; M: male; SD: symptomatic dermographism; DPU: delayed pressure urticaria; LHU: local heat urticaria; ChU: cholinergic urticaria; ColU: cold urticaria; Results of provocation tests: “+” is positive provocation test and “-“ is negative provocation test; patients #4 and #6 had slightly positive provocation tests for DPU and SD, respectively, after omalizumab treatment; **complete response: >90% reduction from baseline in UAS7 score and partial improvement: 30-89% reduction from baseline in UAS7 score; ***fast responder: CSU symptoms regressed within 8 days and slow responder: CSU symptoms regressed after 8 days; ****response after the second injection was determined by physician global assessment based on patient feedback.
FIGURE LEGEND

Figure 1. Patient #4. CSU: before (a) and after (b) omalizumab treatment. Symptomatic dermographism (results of provocation test with FricTest® device): before (c) and after (d) omalizumab treatment.
References