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Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients

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Dear Editor,

Out-of-trial data on long-term safety and predictors of effectiveness of omalizumab (anti-IgE) in chronic urticaria are lacking. We evaluated the outcome of treatment with omalizumab in a large cohort of patients with chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CINDU).

Data were retrieved through retrospective review of patient records from a tertiary dermatological referral centre (Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark). Complete ascertainment of patient records was possible since the

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department keeps track of all administered biological therapy. A consultant dermatologist (SFT) verified the urticaria-diagnosis and assessed response to treatment. MNG and SFT extracted the data and in cases of disagreement, consensus was obtained in the group of authors. According to Danish law, scientific ethics approval is not needed for retrospective chart reviews. Approval for the study was obtained from the National Board of Health (to examine patient records) and from the Data Protection Agency (to save patient data on file). All patients diagnosed with CSU or CINDU who had received at least one injection of omalizumab from 30 June 2010 until 31 Dec 2014 were included in the study. Response to omalizumab treatment was graded according to the degree of relief of symptoms reported by the patient and according to the physician's assessment. It was possible to score the clinical response to treatment with omalizumab for each patient as 'complete or almost complete response', 'partial response' and 'no/limited response' after 3-6 months of treatment. This grading is in accordance with the modified physician's global assessment (PGA) used in other dermatological diseases, where complete or almost complete response corresponds to 90% or more reduction of symptoms; partial response is between 30 and 89% reduction, whereas no/limited response is below 30% reduction in symptoms [1].

154 patients were identified; 110 (71.4%) women and 44 (28.6%) men (Table 1). The majority of the patients were diagnosed with CSU (70.8%). Of these, 30.7% had concomitant angioedema, 34.3% had a positive HR (histamine release) test, and 22.6% had significant comorbidities, the most common being asthma, diabetes, hypertension and hypothyroidism. The 17 patients with CINDU had: delayed pressure urticaria (n=5), cold urticaria (n=5) cholinergic urticaria (n=4), symptomatic dermographism (n=2), and solar urticaria (n=1). The average age at disease onset was significantly higher for CSU patients compared to CINDU patients. Patients with CINDU had, on average a longer duration of symptoms before initiation of treatment with omalizumab compared to patients with CSU. Of all patients

39.6% were previously treated with prednisolone and 26.0% had been treated with dapsone or one or more immunosuppressant drugs such as cyclosporine A, azathioprine, mycophenolate mofetil, methotrexate, and/or TNF-inhibitors. We have previously reported that among a subset of 25 patients with chronic urticaria who were naïve to biologic drugs or who had received omalizumab, 60% obtained complete or almost complete resolution of urticaria and angioedema after onset of therapy with either adalimumab or etanercept, whereas another 15% of our patients experienced partial response to treatment with these TNF-inhibitors [2, 3].

The initial dose of omalizumab given was 150 mg every two weeks in 45.5% of the cases and 300 mg every four weeks in 55.5% of the cases (Table 1). At the time of treatment, omalizumab for CSU was still off-label. Therefore the choice of start dose and duration was based on physician preference and not on a predefined belief of superiority of one treatment regimen over the other. However, of the patients who started on 150 mg every two weeks 82.9% stayed on the same dose and interval throughout the observation period, whereas 5.7% were changed to 150 mg every four weeks due to symptomatic remission, and 11.4% were changed to 300 mg given at intervals every two to four weeks due to symptomatic deterioration. Conversely, of the patients who started on 300 mg every four weeks 86.9% stayed on the same dose and interval throughout the observation period, whereas 6.0% were changed to 150 mg every two to four weeks or to 300 mg every six weeks due to symptomatic remission, and 7.1% were changed to 300 mg given at intervals every two to three weeks due to symptomatic deterioration. Unfortunately, we did not collect data systematically enough to provide estimates of time to response or time to relapse after discontinuation of omalizumab.

A total of 67.4% of the patients with CSU responded completely or almost completely to treatment; 22.2% responded partially, whereas 10.4% had no or limited response to treatment. These numbers are somewhat higher than those observed in the randomized controlled phase III trials of omalizumab in CSU [4-6] but very much in accordance with other real-life studies of response to omalizumab in CSU that have used various measures of effectiveness such as reduction in symptoms, need for rescue medication and validated scoring systems of symptomatic activity [7-10].

Among the patients with CSU, there was a larger fraction of complete or almost complete responders to omalizumab among patients with a negative HR test (77.3 vs. 27.3%), OR=9.07 (2.80-29.32), $p<0.001$; among patients without angioedema (72.3 vs. 56.1%), OR=2.05 (0.95-4.40), $p=0.066$; and among patients with no previous history of treatment with systemic immunosuppressant drugs (71.4 vs. 56.8%), OR=1.91 (0.87-4.17), $p=0.105$. Among patients with these characteristics complete or almost complete response was observed in more than 85%. There was a statistically non-significant tendency for better response to treatment among patients with a late age at onset and a shorter duration of urticaria. There was no significant effect of sex and smoking on treatment response. Also, the effect of omalizumab was not significantly different in patients receiving 300 mg every four weeks compared to patients receiving 150 mg every two weeks (65.8 vs. 68.9%), OR=1.15 (0.56-2.38), $p=0.704$.

Of the 17 patients with CINDU, 9 (52.9%) had complete or almost complete response to treatment; 3 of the 5 patients with delayed pressure urticaria; 2 of the 5 patients with cold urticaria; 3 of the 4 patients with cholinergic urticaria; 1 of the 2 patients with symptomatic dermographism; whereas the patient with solar urticaria had no response to treatment.

A total of 14.3% reported adverse effects during treatment with omalizumab. Reported adverse effects were, in descending order, suspected allergic reactions, gastrointestinal symptoms, injection site reactions, urticaria worsening, headache, dizziness, arthritis, and fatigue. The drug was administered in the outpatient clinic except for a few patients who were treated at home by auto-injection. Patients were monitored 30 minutes after each injection. The suspected allergic reactions occurred during or immediately after administration of the drug but after retrospective evaluation were probably vasovagal syncope and not suspected to be anaphylaxis. Urticaria worsening was only observed in two patients in the weeks after one of the two first injections and was probably related to slow or absence of response to treatment rather than to genuine urticaria worsening. All observed suspected side effects were reversible.

One year after initiation of omalizumab, 56.2% of the CSU patients were still on continuous treatment, while 43.8% had discontinued treatment due to any cause. The median overall drug survival for the first round of treatment (discontinuation due to any cause) in CSU patients was 406 days (325-487 days); 462 days (305-619 days) for women and 364 days (332-496 days) for men, $p=0.412$ for difference between men and women. The most common causes of discontinuation were symptomatic remission or lack of effect, whereas a smaller proportion discontinued due to non-adherence to scheduled ambulatory visits, adverse effects, or pregnancy (Table 2). Of the patients who discontinued treatment with omalizumab due to symptomatic remission 58.3% (14 out of 24) resumed treatment one or more times at a later stage due to recurrence of symptoms. Among these, the effect of omalizumab was comparable to the first round of treatment. Of interest, 10 patients with CSU did not resume treatment with omalizumab due to long-term symptomatic remission and were eventually discontinued from the department. This corresponds to an overall remission rate of 7.3% out of the total of 137 patients with CSU, which is lower than the inferred 1-year

remission rates observed in most [11-13] but not in all previous studies of the natural history of CSU [14].

This real-life study of the effectiveness and safety of treatment with omalizumab in patients with CSU or CINDU showed that around two thirds had complete or almost complete response to treatment with no significant difference in effect between the sexes. Predictors of favourable response to treatment were presence of CSU, no angioedema, negative HR test, older age, shorter duration of symptoms, and no history of treatment with systemic immunosuppressant drugs. In patients with these characteristics complete response to treatment was observed in more than 85% of the cases. It is of novel interest that response to omalizumab is better in patients with a negative HR test, i.e. in patients with non-autoreactive CSU. However, this finding is in accordance with previous studies that have associated longer duration and severity of CSU with the presence of a positive autologous serum test [12]. In a clinical setting, documentation of auto-reactivity in CSU should therefore be accommodated in the decision as to when to deem a patient a non-responder.

This study was retrospective and examined the effect of omalizumab in a single dermatological centre. Furthermore, no validated instruments for measuring urticaria severity such as the Urticaria Activity Score [15] or the Urticaria Control Test [16] were employed to more objectively estimate the effect of omalizumab treatment. Future prospective studies of chronic urticaria should examine in more detail clinical and paraclinical predictors of response and adverse effects of omalizumab.

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Table 1. Characteristics of 154 patients with chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CINDU) treated with omalizumab.

	Total (n=154) N (%)	CSU (n=137) n (%)	CINDU (n=17) n (%)	P-value
Sex				
Women	110 (71.4)	97 (70.8)	13 (76.5)	0.626
Men	44 (28.6)	40 (29.2)	4 (23.5)	
Age at onset	34.8 (15.6)	35.9 (15.4)	25.8 (15.0)	0.012
Age when treated	38.7 (15.0)	39.7 (15.0)	30.6 (13.1)	0.017
Duration	3.9 (5.6)	3.8 (5.4)	4.7 (7.0)	0.531
Angioedema	45 (29.2)	42 (30.7)	3 (17.6)	0.398
Positive HR test	23 (31.5)	23 (34.3)	0	0.168
Smoking	19 (34.5)	18 (38.3)	1 (12.5)	0.239
Comorbidities	33 (21.4)	31 (22.6)	2 (11.8)	0.530
Non-white ethnicity	26 (16.9)	24 (17.5)	2 (11.8)	0.739
Omalizumab start dose				
150 mg/2 weeks	70 (45.5)	62 (45.3)	8 (47.1)	
300 mg/4 weeks	84 (55.5)	75 (54.7)	9 (52.9)	0.888
Montelukast	7 (4.5)	7 (5.1)	0	0.340
Prednisolone	61 (39.6)	58 (42.3)	3 (17.6)	0.050
Other immunosuppressants	40 (26.0)	37 (27.0)	3 (17.6)	0.562

Numbers are calculated from available data.

Table 2. Outcome of treatment one year after initiation of omalizumab in 154 patients with chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CINDU).

	Total (n=154) N (%)	CSU (n=137) n (%)	CINDU (n=17) n (%)
Continuous treatment*	86 (55.8)	77 (56.2)	9 (52.9)
Treatment discontinued (all causes)	68 (44.2)	60 (43.8)	8 (47.1)
Symptomatic remission**	24 (15.6)	22 (16.1)	2 (11.8)
No/limited effect	20 (13.0)	16 (11.7)	4 (23.5)
Non-adherence	13 (8.4)	11 (8.0)	2 (11.8)
Adverse effects	9 (5.8)	9 (6.6)	0
Pregnancy	2 (1.3)	2 (1.5)	0

*Of the patients on continuous treatment a total of 20 patients; 17 with CSU and 3 with CINDU, had been on treatment for shorter than one year by the end of the observation period but had good effect of the treatment and no apparent side effects.

**Of the 24 patients who discontinued treatment within the first year due to symptomatic remission, a total of 14 patients resumed treatment one or more times at a later stage due to recurrence of symptoms.