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LETTER TO THE EDITOR

A Long Term Case Series Study of the Effect of Omalizumab on Chronic Spontaneous Urticaria

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Dear Editor:

Chronic urticaria may seem a trivial disease but it is a challenge for both the patient and the doctor. For the patient the disease is a tormenting itch that leads to social isolation. The volatile nature of the disease makes diagnosing difficult, and taking a comprehensive history is the most important diagnostic tool[1].

The EAACI/GA2LEN/WAO have published two guidelines on the classification and treatment of urticaria[2]. According to the classification guideline spontaneous urticaria can be divided into chronic and acute urticaria depending on whether the symptoms have lasted for more or less than 6 weeks. The chronic types of urticaria are divided into physical urticaria (cold, delayed pressure, vibratory urticaria, and urticaria factitia), other urticaria types (aquagenic, cholinergic, contact urticaria and exercise induced urticaria/anaphylaxis), and finally, spontaneous urticaria. Chronic spontaneous urticarias may be idiopathic (55%) or autoimmune (45%) as defined by the presence of the immunoglobulin (Ig)G anti-IgE receptor, α subunit antibodies, or IgG anti IgE antibodies. The EAACI/GA2LEN/WAO treatment guideline recommends the use of non-sedating antihistamines up to a fourfold dosage as the first line of treatment, followed by leukotriene antagonist, and lastly systemic immunosuppressants or Omalizumab[3].

Omalizumab is an anti-IgE-IgG-antibody, approved for the treatment of allergic asthma, which binds specific IgE molecules, but also reduces the expression of FcεRI on circulating basophils[4]. The mechanism behind the effect on chronic urticaria is more obscure. FcεRI expression on mast cells in the skin is reduced after Omalizumab therapy, thus reducing mast cell activation and histamine release[5].

Urticaria activity is measured by an urticaria activity score of 7 (UAS7), where the number of hives and the itch intensity are each scored on a scale from 0～3 over the preceeding 7 days[6]. The dermatological quality of life index (DQLI) is a questionnaire that measures the impact of dermatological diseases on the quality of life[7]. Until now two randomized placebo controlled studies on the effect of Omalizumab on urticaria, and a large number of case reports comprising 1～20 patients each, have been published (thoroughly reviewed by Ivyanskiy et al.[8]. Taken together, these studies suggest the use of Omlizumab in doses of 150 mg or 300 mg every second or fourth week. The longest treatment period described until now is 15 months.

A total of 15 patients treated with Omalizumab for chronic spontaneous urticaria during 2009～2012 at the Department of Dermatology, Aarhus University Hospital were identified. Previous treatments, concurrent diseases, duration of urticaria, IgE levels (normal＜150) before and during treatment, and basophil histamine release assay (BHRA) results (Histamine release [HR] test, Reflab, Copenhagen, Denmark) were registered. UAS7 and DQLI questionnaires were performed before Omalizumab injections. The dosage was either 150 mg/4 week or 300 mg/4 week depending on weight and serum IgE. In case of a lack of medicinal effect, the dosage of Omalizumab was doubled or intervals between injections were reduced to two weeks.

Of the 15 patients (5 males, 10 females) one was excluded due to lack of registration of UAS7 and DQLI regularly, and 1 patient had no effect on his urticaria after 2 months

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Table 1. Patient characteristics

Patient	Gender	Treatment earlier	Treatment concurrent	BHRA (HR-test)	Concurrent diseases	Adverse events	Duration of illness prior to Omalizumab/ treatment (yr)	Time in Omalizumab treatment (mo)	Dose amount/ frequency of dose	s-IgE (before treatment/ during treatment)	Age at treatment start (yr)	Weight (kg)
1	M	NsAH, SG, SI (My), AB (Ci)		Negative	Asthma	-	1, 5	14	150 mg/ 4th week	Increased/increasing	18	<90
2	F	NsAH, SG, SI (My, S), immunoglobulins, methotrexate, AB (Dx)	NsAH, SI* (My)	Negative	Crohns disease	Headache	8	31	300 mg/ 4th week	Normal/increasing	58	<90
3	F	NsAH, SI (My)	NsAH, SG†, SI* (My)	Negative	-	-	6	8	300 mg/ 4th week	Increased/increasing	21	>90
4	F	NsAH, SG, SI (My, S), immunoglobulins	NsAH, SG†, SI* (My)	Positive	-	-	6	10	150 mg/ 4th week	Normal/increasing	47	<90
5	F	NsAH, SG, TG, AB (Ci)	NsAH	Positive	Diabetes mellitus	-	1	2	150 mg/ 4th week	Normal/increasing	14	<90
6	M	NsAH, SG, TG, SI (S, My), plasmapheresis	SI* (My)	Negative	Asthma	-	13	10	150 mg/ 4th week	Increased/increasing	31	<90
7	F	NsAH, SG, TG, SI (S, My), methotrexate	NsAH, methotrexate	Negative	-	-	8	7	150 mg/ 4th week	Normal/increasing	55	<90
8	F	NsAH, SG, TG, SI (S, My), methotrexate, plasmapheresis, immunoglobulins	NsAH	Negative	Hypertension	-	9	34	300 mg/ 4th week	Normal/increasing	56	>90
9	F	NsAH, SI (My), SG, immunoglobulins	NsAH, SG†, SI (My)	Negative	Fibromyalgia Hypertension Hypercholesterolemia Diabetes mellitus Psoriatic arthritis	Nausea	2	37	300 mg/ 2nd week	Normal/increasing	37	<90
10	M	NsAH, TG, SI (A)	NsAH,	Negative	COLD atrial fibrillation	-	3	23	300 mg/ 4th week	Increased/stable	65	>90
11	F	NsAH, SG, SI (My)	NsAH, SG†	-	Systemic lupus erythematosus Hypertension Osteoporosis	-	15	16	150 mg/ 4th week	Normal/stable	67	<90
12	F	NsAH, SI (My)	NsAH, SG†	Negative	Asthma	-	1	3	300 mg/ 2nd week	Normal/stable	35	<90
13	M	SG, SI (My, A)	NsAH, SG†, SI* (My)	Negative	Osteoporosis	-	3	7	150 mg/ 4th week	Normal/increasing	59	<90
14	M	NsAH, SG, SI (A, Ci)	NsAH, SI* (A)	Positive	Hypertension	-	13	2	150 mg/ 4 weeks	Increased/increasing	44	<90

BHRA: basophil histamine release assay, HR-test: histamine release test, s-IgE: serum immunoglubulin E, M: male, F: female, NsAH: non-sedating antihistamines, SG: systemic glucocorticoids, SI: systemic immunesuppressants, My: mycophenolate mophetil, Ci: cyclosporine A, S: cyclosporine A, TG: topical steroid, A: azathioprine, COLD: chronic obstructive lung disease. *Systemic immunotherapy was tapered down until patients had too many symptoms at the end of the treatment cycle. †In some instances systemic glucocorticoids were given at the beginning of the treatment as a consequence of a severe flare up of urticaria and then tapered off.

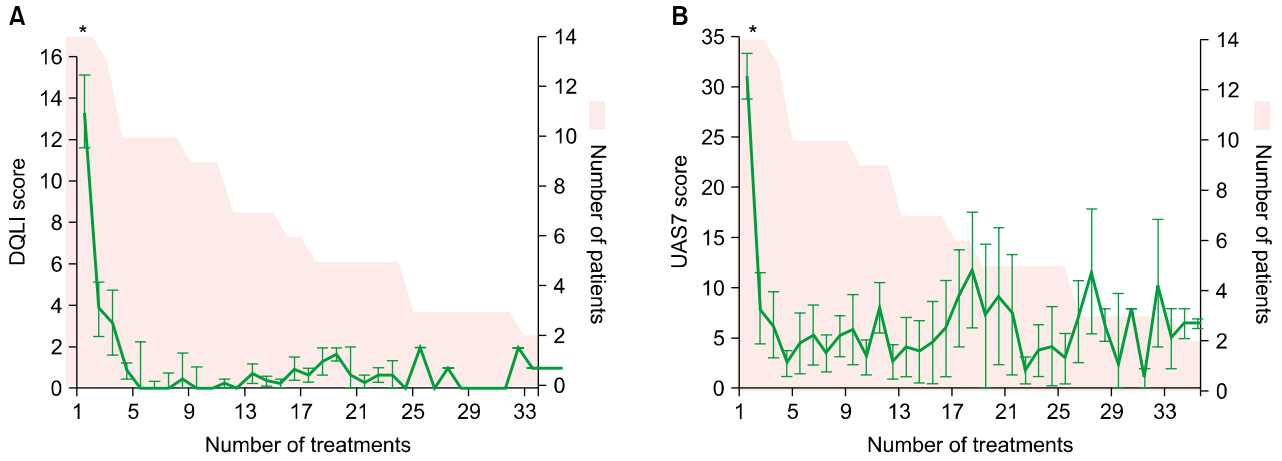

Fig. 1. (A) Average registered with the number of treatments. The shaded area represents the number of patients at the given number of treatment. (B) UAS7 score registered with the number of treatments. The shaded area again illustrates the number of patients. DQLI: dermatological quality of life index, UAS7: urticaria activity score of 7. *$p<0.001$ as calculated by one-way ANOVA for values at treatment number 1, 2 and 3.

(3 injections) and stopped the treatment (patient characteristics can be found as patient number 14). The average duration of urticaria before Omalizumab treatment was 5.9 years (1～15), and the average observation time in Omalizumab treatment was 15.53 months (2～37). Prior therapies with no effect are listed in Table 1 along with concurrent diseases. Three patients had a positive BHRA (Chronic autoimmune urticaria), 10 were negative (Chronic idiopathic urticaria) and 1 was not determined.

The average DQLI demonstrated a significant decrease after the first month from 13.4 to 3.8 ($p<0.001$) and also a further significant decrease after the second month ($p<0.001$), after which it stabilized on a low level (Fig. 1A). UAS7 also showed a significant decrease over the first month from 31.1 to 8.0 ($p<0.001$) (Fig. 1B) after which it stabilized, but standard deviations were high throughout the whole observation period.

Of the 14 patients 5 had increased serum immunoglubulin E (s-IgE) (>150 kU/ml) and 9 had normal levels (Table 1). During the treatment s-IgE was increased (doubled or more) in 11 out of 14 patients ($p<0.01$ using Mann-Whitney-U-test).

The longest documented periods of Omalizumab treatment until now were 15 months. In our material the longest treatment period was 37 months. None of the patients in our study could maintain symptom control without either antihistamines (12 of 14) or another systemic immune suppressant (7 of 14). The significant decrease in DQLI (Fig. 1) demonstrates that Omalizumab is very potent in restoring the patients' quality of life and controlling symptoms. The UAS7 also showed a significant decrease indicating that urticaria activity really is decreased. The high standard deviations reflect that UAS7 was measured in the last week of an injection cycle, where the effect of Omalizumab was wearing off, allowing break through of urticaria symptoms.

An interesting fact is that Omalizumab was efficient independently of s-IgE concentrations, and that s-IgE increased during treatment. The mechanism of this is debated, as is the actual finding. It might be due to the measuring techniques that measure both free and immune-complex bound IgE, thus also Omalizumab bound IgE[9]. Other studies have not been able to reproduce this finding[10]. However chronic spontaneous urticaria, whether autoimmune or idiopathic should by definition be independent of IgE, and it may therefore be the down regulation of FcRεI expression on mast cells and basophils that is important.

In conclusion, this study suggests that omalizumab is an excellent treatment choice for severe treatment refractory urticaria. Omalizumab, however, does not seem to be a cure for the disease only a symptomatic treatment, no matter the cause of urticaria. It is a well known phenomena in patients treated with Omalizumab for allergic asthma that s-IgE may increase[9,10] and we observed the same phenomenon in our patient cohort suffering from chronic urticaria.

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Conglomerated Facial Liposarcoma

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Dear Editor:

Liposarcoma is the most common soft-tissue tumor occurring in adults[1]. Most liposarcomas develop in the deep soft tissues of the extremities and retroperitoneum. Only a very small percentage occurs in the head and neck regions[2]. Although very large liposarcomas are not infrequently found in the intraabdominal regions or extremities, the head and neck liposarcomas mostly occur as small solitary mass which can usually be treated by surgical excision. We report a case of large conglomerated liposarcoma developed on the forehead.

A 74-year old woman presented with firmly palpable nodules on the forehead which had existed for 2 years (Fig. 1). Histopathologic evaluation revealed multivacuolated lipoblasts with nuclear pleomorphism and hyperchromatism scattered in the subcutaneous fat (Fig. 2A, B), which was consistent with the well-differentiated liposarcoma. Immunohistochemical stain with S-100 protein was positive in the adipocytes and some lipoblasts (Fig. 2C), while Ki-67 was negative. The magnetic resonance imaging (MRI) showed a large liposarcoma involving the entire forehead and soft tissues to the level of ethmoid

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