Letter to the Editor

An algorithm for treating chronic urticaria with omalizumab: Dose interval should be individualized

To the Editor:

Successful treatment of recalcitrant urticaria with omalizumab is reported with increasing frequency in the literature.[1-6] Results of a large controlled trial have recently been published,[7] but presently omalizumab is mostly prescribed for urticaria using the guidelines for asthma.[4,5] Little is known about the optimal dose regimen, and therefore the aim of the present study was to develop an algorithm for defining dose, dose interval, and clinical response in different types of urticaria, with the purpose of increasing cost-effectiveness and the quality of life in patients with urticaria, refractory to treatment with high-dose nonsedating H1 antihistamines (nsAH).

Twenty-seven patients (6 children and 21 adults) with a mean age of 34 years (range, 10-65 years) and with recalcitrant urticaria remaining symptomatic despite a high dose of nsAHs were included in the study. All participants were evaluated by using the EAACI Urticaria Activity Score (UAS)[8] at baseline and were required to have a UAS of 6 for inclusion. The mean duration of urticaria was 6 years (range, 1-20 years). All participants had treatment failure on a high dose of nsAHs, and 16 adults had experienced no benefit from treatment with at least one other fourth-line treatment (cyclosporine, azathioprine, methotrexate, prednisolone, mycophenolate mofetil, or ultraviolet B light; Table I).

Chronic spontaneous urticaria was the most common type of urticaria (85%), whereas 22% had delayed pressure urticaria, 11% urticaria factitia (symptomatic dermographism), 7% contact urticaria, and 7% heat contact urticaria. Concomitant allergic diseases were asthma (18%), allergic rhinitis (18%), drug allergy (18%), and anaphylaxis (7%). The most frequent autoimmune diseases, possibly related to chronic urticaria, were diabetes mellitus (11%) and hypothyroidism (11%). There was no correlation between type of urticaria, presence of concomitant disease, serum level of IgE, body weight, or age of the patients and the response to omalizumab treatment (Table I).

Continuing on high-dose antihistamine therapy (3-4 times the recommended dose of desloratadine or fexofenadine), subcutaneous omalizumab (150 mg regardless of serum level of IgE and body weight) was administered every second week. Participants were evaluated by a physician with the UAS at each visit before the administration of the next dose. When the UAS was less than 2, the following dose interval was prolonged to 1 week up to a maximal dose interval of 8 weeks (see flow chart in Fig E1 in this article's Online Repository at www.jacionline.org). If the patient

TABLE I. Characteristics of participants before treatment with omalizumab

ID	Age (y)	Sex	Urticaria type	Duration	Comorbidities	Previous medication	Total IgE (kU/L)	BHR test
1	47	M	DPU, HCU	3 y	ANA, DA		107	0
2	64	M	CSU	20 y	A, DM, DA, HT	MTX	NA	0
3	37	F	DPU	4 y	H, HT	AZA	928	NA
4	36	F	CSU	15 y		LTRA	75.2	0
5	65	F	CSU	4 y		AZA	83.1	0
6	43	F	CSU, UF	5 y		LTRA, CS, AZA	63.4	0
7	16	F	CSU	7 mo		LTRA, CS	141	0
8	23	F	CSU	3 y	ANA	LTRA	82.2	0
9	39	F	CSU, DPU	NA		CS, CsA, AZA	32.1	0
10	14	F	CSU	2 y	A	LTRA, CS	448	0
11	37	M	CSU	4 y		CS, AZA	59.7	0
12	10	M	CSU	1 y		LTRA, CS	94.5	0
13	53	M	CSU	8 y		LTRA, CS, CsA, D	169	0
14	65	F	CSU	18 y	A	AZA	51.4	0
15	12	F	CSU, DPU, UF	3 y			19.4	0
16	24	F	CSU	1 y	DA		450	0
17	19	F	CSU, DPU, HCU	4 y	AR, D, DA	LTRA, AZA, UVB	1824	0
18	52	F	CCU, CU	3 y			97.4	0
19	36	F	CSU	3 y		CS, AZA	131	0
20	47	F	CSU, CU	20 y	D, DA, DM		454	NA
21	14	F	CSU	4 y	DM	LTRA	NA	0
22	32	M	CSU	14 y	AR		NA	NA
23	43	M	CSU	1 y	A	LTRA, CS, AZA	34	0
24	19	F	CCU	3 y	AR, D	LTRA	138	0
25	20	F	CSU, UF	1 y	A, D	LTRA	35.1	NA
26	47	F	CSU, DPU	3 y	AR, H	LTRA, CS, CsA, MTX, D, MMF	118	0
27	12	M	CSU	7 y	AR, H		8.4	1

A, Asthma; *AD*, atopic dermatitis; *ANA*, anaphylaxis; *AR*, allergic rhinitis; *AZA*, azathioprine; *BHR*, basophil histamine release; *CCU*, cold contact urticaria; *CS*, corticosteroid; *CsA*, cyclosporine A; *CSU*, chronic spontaneous urticaria; *CU*, contact urticaria; *D*, dapsone; *D*, depression; *DA*, drug allergy; *DM*, diabetes mellitus; *DPU*, delayed pressure urticaria; *F*, female; *FA*, food allergy; *H*, hypotyroidism; *HCU*, heat contact urticaria; *HT*, hypertension; *LTRA*, leukotriene receptor antagonist; *M*, male; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *NA*, not assessed; *UF*, urticaria factitia; *UVB*, ultraviolet B light.

had a UAS score of 2 or more after 2 or 3 injections of the same dose, the time interval to the next injection was reduced to 1 week and continued at the longest effective "maintenance" interval. In patients with treatment failure (UAS > 3) after 2 to 3 doses of 150 mg of omalizumab, the dose was increased to 300 mg. Patients who had full remission of symptoms after 3 doses of omalizumab injections with 8-week intervals had their treatment paused but were monitored closely for any recurrence of symptoms. In case of recurrence, treatment was restarted and continued with an interval of 8 weeks.

Fifteen patients reached a UAS of less than 2 after 150 mg of omalizumab; 12 of these patients ended up with a dose interval ranging from 5 to 8 weeks while 3 patients continued solely on a high dose of antihistamine without any relapse (see Fig E2 in this article's Online Repository at www.jacionline.org). The remaining 12 patients failing to reach a UAS of less than 2 on 150 mg of omalizumab continued treatment with 300 mg. Four of them had treatment failure after 2 to 3 doses on 300 mg, whereas 8 patients ended on a dose interval of 4 to 8 weeks on 300 mg. In 2 of these 8 patients, treatment was paused after the 8-week interval had been reached, but both experienced relapses within 7 and 16 weeks, respectively, and were restarted on treatment with 300 mg of omalizumab. Consistent with the emerging data,[7] omalizumab seems highly efficacious and a promising therapy in the treatment of various types of chronic urticaria including chronic spontaneous urticaria[2] and physical urticarias with diverse etiologies such as cold contact urticaria[3] and delayed pressure urticaria.[4] In contrast to the dosing scheme of omalizumab in asthma treatment,[9] in which the dose adjustment is based on body weight and screening IgE, adjustments seem unnecessary for successfull treatment of recalcitrant urticaria.

The algorithm of individualizing treatment with omalizumab proved efficient, was well tolerated, and provided a decrease in the frequency of hospital visits, thereby being more cost-effective for the society and convenient for the patient. Regardless of dose, no safety issues or concerns were revealed during the study. We therefore suggest that patients with recalcitrant urticaria not responding to conventional treatment should be treated with omalizumab in an individualized regimen as described above. For economic reasons, treatment should, however, be restricted to recalcitrant cases where systemic treatment with fourth-line drugs such as cyclosporine, methotrexate, dapsone, or mycophenolate has proven ineffective or not feasible.

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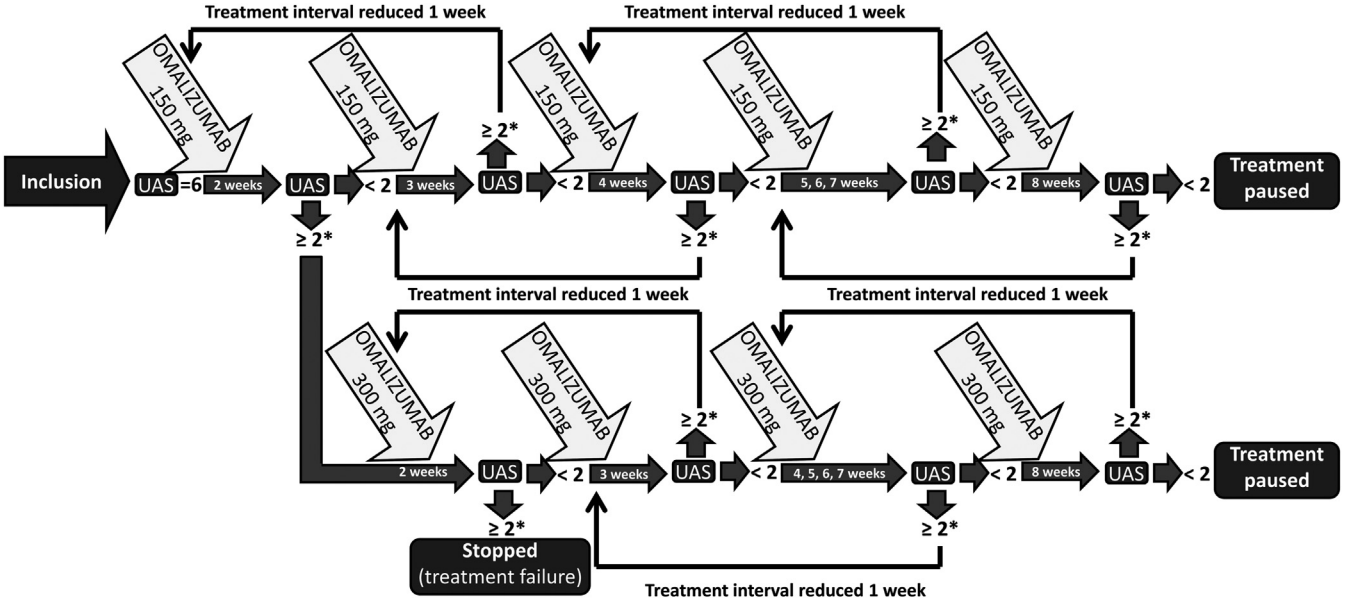


FIG E1. Flow chart of the algorithm for omalizumab treatment. *Same time interval was tried 2 to 3 times in case of the UAS being 2 or more before the treatment interval was reduced by 1 week.

ID	Maximal dose interval (weeks) 2	3	4	5	6	7	8	Total treatment duration	Total number of injections	UAS score after last treatment
	Drug dose 150 mg									
1				M				91	25	1
2				M				112	29	0
3						M		58	16	N.A.
4						M		36	11	0
5						M		78	16	0
6						M		101	28	5
7						M		28	9	0
8							M	63	14	0
9							M	156	26	1
10							M	89	17	0
11							M	90	17	1
12							M	37	10	0
13							Paused	100	16	0
14							Paused	62	11	0
15							Paused	35	10	0
	Drug dose 300 mg									
16							M*	119	27	0
17							M*	95	18	0
18							M	138	28	0
19						M		133	31	0
20					M			20	7	0
21					M			45	17	3
22				M				23	10	4
23			M					28	11	2
24	Failure							9	6	6
25	Failure							3	4	6
26	Failure							18	8	6
27	Failure							11	7	5

FIG E2. Treatment algorithm with omalizumab. *M*, Maintenance; *NA*, not assessed. *Treatment restarted (after pausing) because of relapses.