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REFERENCES

1. Akdis M. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol.* 2006;18:738-744.
2. Siroux V, Lupinek C, Resch Y, et al. Specific IgE and IgG measured by the MeDALL allergen-chip depend on allergen and route of exposure: the EGEA study. *J Allergy Clin Immunol.* 2017;139:643-654.
3. Chapman MD, Platts-Mills TA. Measurement of IgG, IgA and IgE antibodies to Dermatophagoides pteronyssinus by antigen-binding assay, using a partially purified fraction of mite extract (F4P1). *Clin Exp Immunol.* 1978;34:126-136.
4. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol.* 1979;122:2218-2225.
5. Smith AM, Yamaguchi H, Platts-Mills TA, Fu SM. Prevalence of IgG anti-Der p 2 antibodies in children from high and low antigen exposure groups: relationship of IgG and subclass antibody responses to exposure and allergic symptoms. *Clin Immunol Immunopathol.* 1998;86:102-109.
6. Aalberse RC, Platts-Mills TA. How do we avoid developing allergy: modifications of the T_H2 response from a B-cell perspective. *J Allergy Clin Immunol.* 2004;113:983-986.
7. Davies JM, Platts-Mills TA, Aalberse RC. The enigma of IgE+ B-cell memory in human subjects. *J Allergy Clin Immunol.* 2013;131:972-976.
8. Aalberse RC, Platts-Mills TA, Rispens T. The developmental history of IgE and IgG4 antibodies in relation to atopy, eosinophilic esophagitis, and the modified T_H2 response. *Curr Allergy Asthma Rep.* 2016;16:45.
9. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet.* 2001;357:752-756.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Efficacy of omalizumab 150 mg/month as a maintenance dose in patients with severe chronic spontaneous urticaria showing a prompt and complete response to the drug

To the Editor,

Chronic spontaneous urticaria (CSU) is a rather frequent disorder that may severely disturb patient's quality of life. Most patients respond properly to second-generation antihistamines at a licensed or at a higher than licensed dosage.¹ However, a minority of patients seem insensitive to antihistamine treatment at any dosage; for these subjects, alternative treatments must be prescribed to control the disease. The recent EAACI guidelines for the diagnosis and management of CSU recommend omalizumab, a humanized anti-IgE

monoclonal antibody, as the first choice for such patients in view of its excellent safety profile and the high rate of success.¹ Phase three, double-blind, placebo-controlled studies²⁻⁴ have identified a monthly dose of 300 mg as the optimal dosage to treat antihistamine-resistant patients. As the drug is not a disease-modifying one, a large proportion of patients relapse after the treatment are stopped. The optimal duration of the treatment has not been established yet, although recent studies have shown its safety and efficacy up to 48 weeks (1 year).⁵ However, some patients showing an excellent

response to the drug relapse even after such prolonged treatment period and need to be treated for longer times. Nonetheless, recent studies have shown that omalizumab retreatment is effective and safe in patients who responded to the initial treatment.⁶⁻⁸

The Italian Medical Agency (AIFA; Agenzia Italiana del Farmaco) has established that in CSU, omalizumab can be given at the dose of 300 mg/month for six times, with the possibility to resume the treatment for further 5 months in case of relapse after a stop of 2 or more months. After the end of the second course, the treatment is no longer reimbursed by the National Health Service and has therefore to be stopped. Such policy raises several ethical and practical problems involving both patients and doctors. The high cost of the drug and its unavailability outside the hospital environment represent an important obstacle on one hand, while on the other hand, doctors must cope with the problem of being forced to prescribe much more toxic drugs, such as cyclosporine,¹ an off-label drug for CSU, in patients who experienced a complete response to omalizumab just some months before. Although formal safety studies beyond 1 year of therapy with omalizumab in CSU patient are currently missing, recent data from real-life studies suggest that most patients with a baseline severe CSU who relapse after 1 year of treatment can be treated for at least another year.⁶ Further, it must be considered that in patients with severe asthma, omalizumab treatment is not subjected to any time restriction.

In view of the current Italian rules and to the unavailability of the drug beyond one year of treatment, a prospective real-life study was started to investigate the effect of a reduction of omalizumab

dose to 150 mg/mo as a maintenance therapy in relapsing patients showing a complete response to the dose of 300 mg with the aim to prolong their treatment period as much as possible. Notably, a monthly dose of 150 mg, although possibly less effective than 300 mg in a proportion of patients,²⁻⁴ is currently employed in several settings.^{2,5,9}

The study was carried out on 14 patients (M/F 5/9; mean age: 49.5 years, range: 37-71 years; mean disease duration: 51 months, range: 2-200 months) with severe CSU (baseline UAS7 > 30) unresponsive to antihistamines at a dose three times higher than the licensed dose and relapsing 2 months after the completion of the first course of omalizumab 300 mg/mo for 6 months to which they had shown a complete response (UAS7 < 6). All patients were classified as "early responders" to omalizumab as the clinical effect of the drug was already evident within the first month after the first administration. After resuming the treatment at the dose of 300 mg/mo for one time to re-induce a complete response, patients were treated with 150 mg/mo of omalizumab as an add-on treatment to second-generation antihistamine at a licensed dose and evaluated after 4 months of this therapeutic regimen. The response to the treatment at a reduced dosage was plotted against disease duration, the presence of angioedema, baseline UAS7 value, the presence of thyroid autoimmunity (either thyroperoxydase or thyroglobulin), and baseline levels of D-dimer, ESR, and CRP.

All patients gave an informed written consent after having been clearly explained that the reduced dosage of the drug had to be considered as off-label and that the goal of the study was to potentially

TABLE 1 Baseline characteristics of the study population and response to omalizumab

	Sex	Age	DD	AE	ESR	CRP	Thyroid	D-dimer	UAS7 Baseline	UAS7 300	UAS7 150
1	F	47	18	Yes	36	1.3	TPO	1200	38	0	20
2	M	65	18	Yes	Neg	1.0	Neg	1815	36	0	18
3	M	67	180	Yes	Neg	Neg	Neg	305	35	0	18
4	F	37	88	Yes	Neg	Neg	Neg	3764	38	0	16
5	F	53	24	Yes	Neg	1.29	Neg	2520	35	0	14
6	F	45	80	Yes	Neg	Neg	TPO	825	40	0	20
7	M	55	9	No	Neg	Neg	TG	410	37	0	20
8	M	30	3	No	Neg	Neg	TPO	356	32	0	0
9	F	49	2	No	Neg	Neg	Neg	1005	33	0	0
10	F	46	200	Yes	Neg	1.15	Neg	1560	30	0	0
11	F	39	7	No	37	2.66	Neg	1484	34	0	0
12	F	71	60	No	Neg	1.44	Neg	805	37	0	0
13	F	39	4	Yes	Neg	Neg	Neg	198	36	0	0
13	M	50	24	No	Neg	Neg	Neg	450	34	0	0

Patients 1-7: worsened halving omalizumab dose. Patients 8-14 unchanged halving omalizumab dose.

DD: disease duration in months. AE: presence of angioedema episodes. ESR: erythrocyte sedimentation rate (normal if < 30 mm). CRP: C-reactive protein (normal if < 0.3 mg/dl). Thyroid: presence of thyroid autoimmunity (TPO: thyroperoxydase; TG: thyroglobulin). D-dimer: values expressed as ng/ml (normal if < 500).

UAS7 Baseline: UAS7 score before starting omalizumab treatment. UAS7 300: UAS7 score during week 4 after resuming omalizumab at the dose of 300 mg/month. UAS7 150: UAS7 score during week 4 after the 4th administration of omalizumab 150 mg/month. UAS7 300 and UAS 150 scores were evaluated while taking second-generation antihistamine at licensed dose.

prolong the duration of the treatment before considering a shift to more toxic drugs in case of relapse. The study was approved by the Internal Review Board of the Clinic.

The baseline features of the study patients along with the clinical response to the treatment are shown in Table 1. Seven of 14 patients (50%) showed an ongoing complete control of the disease (UAS7 < 6) despite halving the monthly dose of omalizumab. In the remaining seven patients, the dose reduction was associated with a worsening of the disease (UAS7 score between 7 and 21), although in no case, it returned to the baseline severity. The partial loss of response to the drug did not depend on disease duration, the presence of thyroid autoimmunity, or baseline ESR, CRP, or D-dimer, whereas it was associated with the baseline severity of the disease ($P < 0.05$). Also, a history of angioedema was much more frequent among those who worsened following the reduction in omalizumab dosage (6/7, 86%) than in patients who maintained the control of the disease (2/7; 29%), but due to the small number of patients, the difference did not reach the statistical significance.

Although studies on larger number of patients are needed to confirm these observations and despite the limitation of being non-randomized, the present real-life study suggests that it is possible to halve the costs of omalizumab maintenance treatment in about one half of patients with severe CSU showing a prompt response to the drug at the dose of 300 mg/mo without any loss of clinical efficacy. Patients who worsen with a reduced dosage of omalizumab are in general those showing a more severe diseases at baseline as well as those with a history of angioedema associated with the wheals. This is in keeping with previous observations that in patients with angioedema, only the dosage of 300 mg/month seems to be effective.² Whether the reduction in omalizumab dosage as a maintenance therapy will work also in patients showing a delayed response to the drug remains to be established. In conclusion, this study confirms previous observations in a very small number of patients¹⁰ that a maintenance monthly dose of 150 mg of omalizumab may be sufficient to guarantee an ongoing control of the disease in a large proportion of patients with CSU showing an early response to the drug.

CONFLICTS OF INTEREST

The author declares that they have no conflicts of interest.

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REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. *Allergy*. 2018;73:1145-1146.
2. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
3. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H₁ antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135:67-75.
4. Maurer M, Kaplan A, Rosén K, et al. The XTEND-CIU study: long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2018;141:1138-1139.
5. Vadasz Z, Tal Y, Rotem M, et al. Israeli Forum for investigating and treating chronic spontaneous urticaria (CSU). Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. *J Allergy Clin Immunol Pract*. 2017;5:1743-1745.
6. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with Omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol*. 2014;150:288-290.
7. Turk M, Yilmaz I, Bahcecioglu SN. Treatment and retreatment with omalizumab in chronic spontaneous urticaria: real life experience with twenty-five patients. *Allergol Int*. 2017;67:85-89.
8. Mandel VD, Guanti MB, Liberati S, Demonte A, Pellacani G, Pepe P. Omalizumab in chronic spontaneous urticaria refractory to conventional therapy: an Italian retrospective clinical analysis with suggestion for long term Maintenance strategies. *Dermatol Ther (Heidelb)*. 2018;8:291-301.
9. Sussman G, Hébert J, Gulliver W, et al. Insights and advances in chronic urticaria: a Canadian perspective. *Allergy Asthma Clin Immunol*. 2015;11:7.
10. Romano C, Sellitto A, De Fanis U, et al. Maintenance of remission with low-dose omalizumab in long-lasting, refractory chronic urticaria. *Ann Allergy Asthma Immunol*. 2010;104:95-97.

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A missense mutation of the plasminogen gene in hereditary angioedema with normal C1 inhibitor in Japan

To the Editor,

Hereditary angioedema with normal C1 inhibitor (HAEnCI) is a novel type of HAE, whose genetic background is heterogeneous.¹

Mutations in the factor XII (F12) gene have been reported almost exclusively in Caucasians,²⁻⁶ whereas none have been reported for other races, including Asians. The genetic abnormalities that cause