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Omalizumab is effective in symptomatic dermographism—results of a randomized placebo-controlled trial

To the Editor:

Symptomatic dermographism (SDerm) is the most common form of physical urticaria with a prevalence of up to 5%.[1] SDerm is characterized by itchy wheals that occur in response to friction, for example, after rubbing or scratching of the skin, and usually last for 1 to 2 hours.[2] SDerm commonly lasts for years and significantly impairs quality of life (QOL).[2] The underlying cause of SDerm is unknown, and the trigger is difficult, if not impossible, to avoid. Therefore, symptomatic treatment with antihistamines is the first-choice treatment. However, higher than standard doses are usually required to achieve symptom control, and some patients do not respond to updosing of antihistamines.[2]

Omalizumab, a humanized anti-IgE antibody, is highly effective in antihistamine-refractory patients with chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, and the drug was licensed for use in CSU/chronic idiopathic urticaria in 2014. Case reports suggest that patients with physical urticaria including SDerm can also benefit from omalizumab treatment.[3,4] Here, we report the results of a phase 2 trial with patients with SDerm, in which we evaluated the efficacy and safety of 2 different doses of omalizumab as compared with placebo.

Overall, 61 patients with SDerm were randomized, received at least 1 treatment, and were included in the safety analyses, and 55 were included in the primary end-point analysis (for details on study procedures, see this article's Online Repository and Fig E1 at www.jacionline.org). The baseline, demographic, and clinical characteristics were comparable in all groups (see Table E1 in this article's Online Repository at www.jacionline.org). Most notably, the mean Dermatology Life Quality Index (DLQI) score at baseline was 11.1 (Table E1), that is, a score that indicates a very large effect on QOL.[5]

Critical friction thresholds (the strongest trigger strength, at which a patient developed symptoms) at week 10 (primary readout) were significantly improved in the omalizumab 150 mg (-1.8 ± 0.4; $P = .014$) and 300 mg (-2.0 ± 0.4; $P = .004$) groups, as compared with the placebo group (-0.6 ± 0.3; Fig 1, *A*). Both omalizumab 150 mg and 300 mg resulted in a rapid improvement in friction thresholds, as early as in week 4 after the start of treatment (Fig 1, *B*). After the last injection, during the follow-up period, provocation trigger thresholds in the omalizumab groups increased and did not show differences to those in the placebo group 6 weeks after the last treatment. No significant differences between 150 mg and 300 mg omalizumab groups were observed at any time during the study (Fig 1, *A* and *B*).

To test whether patients with SDerm with low and high trigger thresholds and disease activity show differences in their responses to omalizumab, we assessed threshold values in every patient at

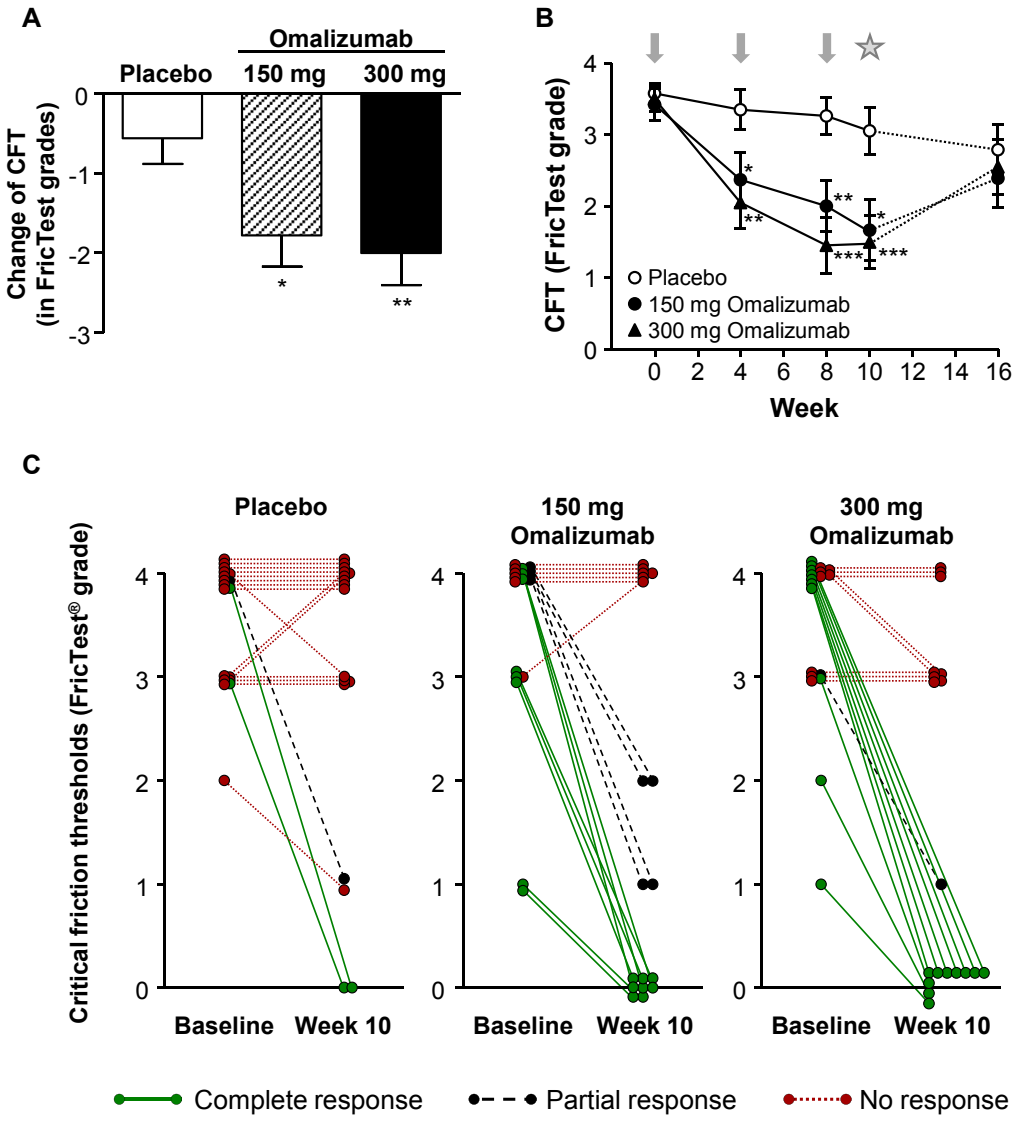

FIG 1. Omalizumab markedly reduces trigger thresholds in SDerm. Omalizumab 150 mg, omalizumab 300 mg, or placebo was injected subcutaneously 3 times every 4 weeks and critical friction thresholds (CFTs) were assessed using FricTest. Data are presented as mean reduction in CFTs from baseline at the primary end point at week 10 **(A)** and mean absolute values at every investigated time point **(B)**, with error bars indicating SEMs. The *arrow* indicates time of injection, and the *star* indicates the primary end point readout 2 weeks after the last injection. **C,** Individual provocation thresholds before and after treatment. $*P < .05$, $**P < .01$, and $***P < .005$.

baseline and 10 weeks later. As shown in Fig 1, *C*, patients with SDerm with low and high baseline thresholds showed similar responses to omalizumab treatment. Two of 18 (11%) patients with SDerm showed complete response at week 10 after placebo treatment, whereas 8 of 18 (44%) showed complete response to 150 mg omalizumab. With omalizumab 300 mg, 10 of 19 (53%) showed complete response (Fig 1, *C*). No response at all was observed in 15 of 18 (83%) patients treated with placebo, 6 of 18 (33%) patients treated with omalizumab 150 mg, and 8 of 19 (42%) patients treated with omalizumab 300 mg (Fig 1, *C*).

The frequency of adverse events was similar across all groups. The frequency of serious adverse events was low, with 1 event in the 150 mg omalizumab group, 1 in the 300 mg omalizumab group, and 1 in the placebo group (see Table E2 in this article's Online Repository at www.jacionline.org); none of them was considered related to the study medication.

Patients with SDerm refractory to antihistamine treatment were considerably impaired in their QOL (Table E1). Treatment with both 150 mg and 300 mg omalizumab improved the QOL as assessed by mean DLQI scores at week 10 compared with baseline (Fig 2, *A* and *B*). Overall, 13 of 18 (72%) patients treated with 150 mg omalizumab and 11 of 19 (58%) patients treated with 300 mg omalizumab improved at least 4 points in the DLQI scale, the minimal clinically important difference.[6] In contrast, only 6 of 19 (32%) placebo-treated patients improved by 4 or more points.

Taken together, we found pronounced, statistically significant, and clinically meaningful reductions in disease activity and impact in patients with SDerm treated with omalizumab 150 or 300 mg. The risk/benefit profile for omalizumab was good (Table E2) and did not show any new safety aspects as compared with previously published trials.

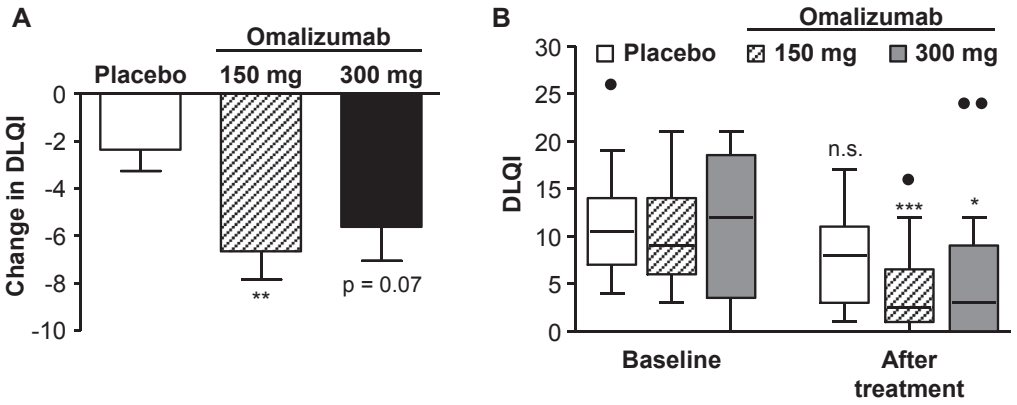

FIG 2. Omalizumab treatment improves QOL in patients with antihistamine-refractory SDerm. **A,** Mean change in DLQI scores assessed at week 10 (primary end point) to baseline, with error bars indicating SEMs. **B,** DLQI scores assessed at baseline and at 10 weeks after start of treatment, presented as box-and-whiskers showing median, upper and lower quartile in the box and whiskers indicating 1.5 times the interquartile range (Tukey). *n.s.,* Not significant. $*P < .05$, $**P < .01$, and $***P < .005$.

Interestingly, both doses of omalizumab, 150 mg and 300 mg, were effective, with no statistical differences between them. This is in contrast to CSU, in which both doses are also effective, but 300 mg omalizumab is more effective than 150 mg.[7,8]

It is, as of yet, unclear why omalizumab has these strong effects on disease activity in SDerm. A comparison of baseline characteristics in responders and partial or nonresponders (see Table E3 in this article's Online Repository at www.jacionline.org) revealed no statistically significant differences between the 2 groups. Passive serum transfer experiments have suggested that a soluble transferable factor, presumably IgE, is involved in the pathogenesis of physical urticaria forms such as SDerm, cold urticaria, or solar urticaria.[9] But as of now, no relevant role of IgE in any of these diseases has been proven.[10] Future clinical trials with more patients will have to be performed to identify potential subgroups that can predict a response to omalizumab treatment in SDerm.

Future studies are needed to characterize the role of IgE in the pathogenesis of SDerm and the mechanisms of action of omalizumab in SDerm and other physical urticarias. Also, additional controlled trials are needed to test whether omalizumab is similarly effective in other physical urticaria types such as solar, heat, or pressure urticaria, all of which have been described in case reports to respond to omalizumab. Furthermore, future trials with larger numbers of patients need to provide more detailed information on the time to response after omalizumab treatment and the optimal doses used in the treatment of patients with physical urticaria.

In conclusion, omalizumab in doses of 150 and 300 mg resulted in a high rate of complete and partial responders in patients with SDerm and a pronounced overall reduction in disease activity and QOL impairment in these patients. The results of our study show that patients with SDerm unresponsive to antihistamine treatment can benefit from well-tolerated and effective treatment with omalizumab.

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Defective protein prenylation is a diagnostic biomarker of mevalonate kinase deficiency

To the Editor:

Mevalonate kinase (MVK) deficiency (MKD) is a rare, autosomal-recessive autoinflammatory disease that presents in its milder form as hyper-IgD syndrome (HIDS), and in the most severe cases as mevalonic aciduria (MVA).[1] It is widely assumed that the inflammatory symptoms of MKD are caused by defective protein prenylation owing to hypomorphic mutations in MVK. Prenylation is a posttranslational modification of proteins, particularly small GTPases, with isoprenoid lipids that are generated via the mevalonate biosynthetic pathway[2] (Fig 1, *A*). Two recent studies in *Nature Immunology* suggested that loss of the prenylated small GTPases RhoA or K-Ras in MKD results in activation of the pyrin inflammasome and IL-1β secretion.[3,4] However, although MVK is essential for synthesis of the isoprenoid lipid geranylgeranyl diphosphate needed for the prenylation of Rab-, Rho-, and other families of small GTPases (Fig 1, *A*), numerous studies have been so far unable to convincingly demonstrate directly that prenylation of small GTPases is actually altered in MKD. To provide this missing mechanistic evidence, we developed a highly sensitive *in vitro* prenylation assay that enables the detection of unprenylated small GTPase proteins in cell lysates.[5,6] The *in vitro* prenylation assay involves the incorporation of a biotinylated isoprenoid lipid into unprenylated proteins in cell lysates when incubated with a recombinant geranylgeranyl transferase (GGTase) enzyme—either GGTase I (that prenylates Rho, Rac, and Rap proteins) or GGTase II (that prenylates Rab proteins). The small GTPases that are prenylated (and thereby biotinylated) in the *in vitro* prenylation reaction can then be detected with streptavidin after blotting onto membranes.[5,6] We also used western blotting to specifically detect unprenylated Rap1A.[5,7] Both these approaches demonstrated a striking accumulation of unprenylated 21- to 27-kDa Rab proteins and unprenylated 21-kDa Rap1A in PBMCs from an 8-year-old boy with HIDS (V377I/H20N genotype), which was absent in either of his heterozygous, healthy parents (Fig 1, *B*). Furthermore, freshly isolated PBMCs from this patient and 2 other patients with HIDS (MKD1, 2, 3 in Fig 1, *C*) who were compound heterozygous or homozygous for the commonest mutation, V377I, all showed an accumulation of unprenylated Rab GTPases. This was not due simply to an overall increase in the level of Rab proteins because western blot analysis of Rab 14 did not show an increase in patients with MKD (see Fig E1 in this article's Online Repository at www.jacionline.org). Consistent with this, we recently used a quantitative proteomic approach to show that the accumulation of unprenylated Rab proteins in HIDS cell lines was not due simply to a larger pool of Rab proteins.[6]

The accumulation of unprenylated Rab proteins seen in MKD PBMCs was absent in healthy controls and patients with other autoinflammatory diseases such as familial Mediterranean fever, cryopyrin-associated periodic syndrome, and TNF receptor–associated periodic syndrome (Fig 1, *C*; genotypes are shown in Table E1 in this article's Online Repository at www.jacionline.org). The defect in protein prenylation in MKD cells was least obvious in cells from a homozygous V377I patient, consistent with the more variable (and sometimes absent) clinical phenotype of these individuals.[8] However, analysis of PBMCs from this patient on a separate blot, using more protein, revealed a subtle but clear accumulation of unprenylated Rab proteins compared with PBMCs from an unaffected control (Fig 1, *D*).

Unprenylated Rap1A, and unprenylated 21-kDa GTPases that are also substrates for GGTase I,[5,6] such as Rho, Rac, and K-Ras, could be clearly detected in only 1 compound heterozygous patient with HIDS (MKD 1 in Fig 1, *C*) and were not observed in PBMCs from healthy controls or from patients with other autoinflammatory diseases (Fig 1, *C*). The detection of unprenylated Rab proteins in MKD PBMCs therefore appears to be a more sensitive indicator of defective prenylation than detection of unprenylated Rap1A or other proteins modified by GGTase I.

To our knowledge, these analyses are the first direct demonstration that protein prenylation is defective in patients with MKD. The accumulation of unprenylated proteins in fresh PBMCs therefore appears to be a useful diagnostic biomarker to distinguish MKD from other childhood autoinflammatory disorders. Importantly, none of the 3 HIDS/MKD patients analyzed (Fig 1, *B-D*) were undergoing an inflammatory flare at the time of blood collection and were not receiving treatment. Furthermore, we did not find any defect in prenylation in PBMCs from patients treated with statins or bisphosphonate (see Fig E2, *A* and *B*, and Table E2 in this article's Online Repository at www.jacionline.org), 2 widely used classes of drug that also inhibit the mevalonate pathway[7] (Fig 1, *B*). Defective protein prenylation therefore appears to be a specific hallmark of MKD.

We also analyzed a panel of cultured EBV-transformed lymphoblast cell lines (LCLs) derived from patients with the severe (MVA) or milder (HIDS) form of MKD. In contrast to fresh PBMCs from patients with HIDS (Fig 1, *B-D*), the MVA LCLs showed little or no defect in the prenylation of Rab GTPases when the cells were cultured at 37°C (Fig 1, *E*). However, when

METHODS

We performed an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of omalizumab (150 or 300 mg every 4 weeks) over 16 weeks in 61 adult patients with antihistamine-resistant SDerm (SDerm, UFO trial). The trial was conducted by the urticaria clinics of 3 German university hospitals (Berlin, Mainz, and Freiburg) and in accordance with the Declaration of Helsinki. All relevant ethics committees and the German regulatory authority for monoclonal antibodies (Paul Ehrlich Institut) approved the study protocol. The study was registered with EudraCT (EudraCT no. 2011-005615-87) and with ClinicalTrials.gov (NCT 02169115) before its start. Participants were recruited from December 1, 2012, to December 31, 2014.

Patients

All patients had to be and were between 18 and 75 years old, with a history of 6 months or longer of SDerm refractory to antihistamine treatment. Exclusion criteria included a treatment with systemic steroids, cyclosporine, methotrexate, dapsone, or other immunosuppressives within the 4 weeks before the study, the use of any antihistamine or leukotriene antagonist 4 days before visit 1, a history of malignancies during the 5 years before the screening visit, previous treatment with omalizumab, and pregnancy. All patients provided written informed consent before enrollment.

Of the 61 patients enrolled, 55 were included in the primary end-point analysis. Patients who left the study did so because of a lack of efficacy (1 each in the placebo and omalizumab 150 mg group), relocation (n = 1, placebo), and because the study medication expired (n = 1, omalizumab 300 mg). In 2 patients, the primary outcome could not be assessed because baseline measurements of provocation thresholds failed (1 placebo, 1 omalizumab 300 mg).

Randomization and masking

Following a screening period of 1 to 2 weeks, patients were assigned at random and a 1:1:1 ratio to receive omalizumab 150 mg, omalizumab 300 mg, or placebo, without any stratification. Patients were recruited and included into the study by the respective study centers and randomized centrally to the treatment arms on the basis of a randomization list provided by the study drug provider (Novartis, Basel, Switzerland), who was not involved in the rest of the trial. Study medication blinding was achieved by the use of placebo, which contained the same ingredients as the omalizumab formulation, excluding omalizumab. There were no evident differences between omalizumab and placebo, other than their viscosity. Because of this, a separate and independent unblinded study team prepared and injected the study medication. This unblinded team had no study-specific communication with the blinded study team and was not involved in any other parts of the trials.

Procedures

Each patient received 3 subcutaneous injections of 150 mg omalizumab, 300 mg omalizumab, or placebo every 4 weeks, with the primary readout 2 weeks after the last injection. This 10-week treatment phase was followed by a follow-up period of 6 weeks. At the end of weeks 0, 4, 8, 10, and 16, patients underwent provocation tests at the study center to assess SDerm trigger thresholds. In SDerm, shear forces on the skin are responsible for the occurrence of clinical signs and symptoms. To assess provocation thresholds in patients with SDerm, we used FricTest (MOXIE GmbH, Berlin, Germany), which is an objective and validated tool for standardized and reproducible provocation testing.[E1]

Outcomes

The primary outcome was the change, from baseline to week 10 of the treatment period, in critical friction thresholds (CFTs) determined by provocation testing. Secondary outcomes included the safety of patients treated with omalizumab, the long-term effects of omalizumab on the reduction in trigger thresholds, changes in QOL impairment, and the rate of complete and partial responders to omalizumab. Safety was evaluated by recording and monitoring the frequency of treatment-emergent adverse events and serious adverse events. Long-term effects were assessed 8 weeks after the last injection of study drug. *Complete response to treatment* was defined as the absence of a positive test response to the strongest friction strength (grade 4) tested, at the end of week 10 after the start of treatment. *Partial response* was defined as a reduction of 2 or more FricTest grades in CFTs.

Statistical analysis

The UFO study is the first clinical trial of the efficacy and safety of omalizumab in SDerm. Therefore, no pretrial sample size calculation was performed. Baseline demographic data and clinical characteristics are expressed as frequencies (n) and percentages (%) for sex, median and interquartile range for age, and mean ± SD for body mass index, provocation thresholds, and duration of disease. Continuous variables, that is, changes from baseline in provocation thresholds at week 10 (primary end point) as well as CFTs at different time points during the study course, are expressed as means ± SEMs. Categorical data (responder rates) are presented as frequencies (n) and percentages (%).

The primary end point (change in provocation trigger thresholds) was analyzed by 1-way ANOVA. In case of a significant result, all 3 treatment arms were compared without correction for multiple testing by using the unpaired Student *t* test. The latter was also applied for the comparison of the CFT at different time points during the study course. In all analyses with the unpaired Student *t* test, *P* values were chosen from the test performed either for "equal variances assumed" or for "equal variances not assumed," depending on the Levene test for equality of variances. The responder distribution at week 10 was compared between treatment arms with the chi-square test. The statistical program used was IBM SPSS Statistics Version 22, IBM, Ehningen, Germany.

All efficacy analyses were done in the per-protocol population. Safety analyses were performed in all participants who received at least 1 dose of study drug.

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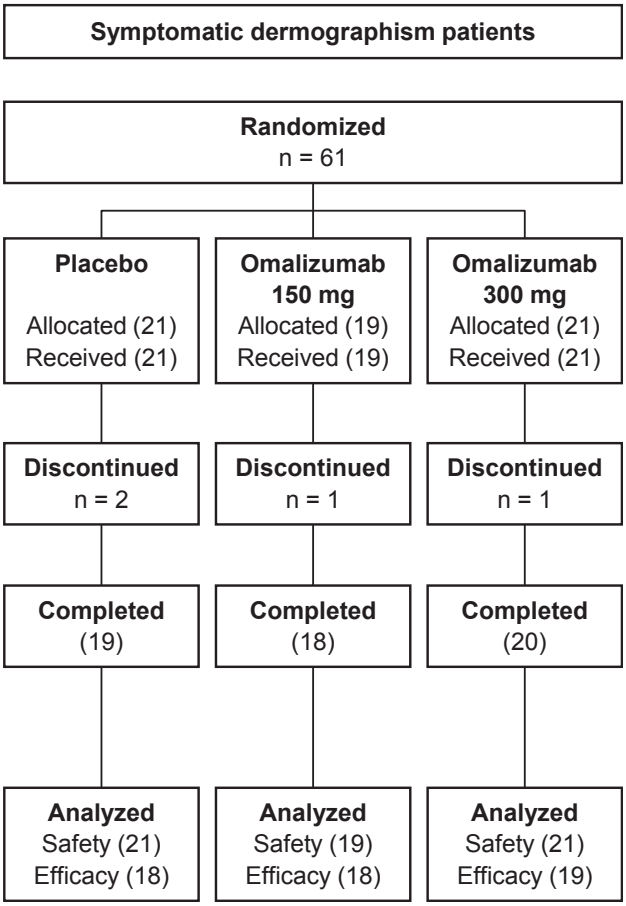

FIG E1. Trial profile.

TABLE E1. Baseline demographic and clinical characteristics of the intention-to-treat population by treatment group

	Patients with SDerm			
Characteristic	**All patients (n = 61)**	**Placebo (n = 21)**	**Omalizumab 150 mg (n = 19)**	**Omalizumab 300 mg (n = 21)**
Sex				
Male	27 (44)	9 (43)	6 (32)	12 (57)
Female	34 (56)	12 (57)	13 (68)	9 (43)
Age (y)	40 (30-50)	37 (26-46)	45 (34-52)	40 (31-51)
BMI (kg/m^2)	25.8 ± 4.7	25.1 ± 4.8	26.6 ± 5.5	25.6 ± 3.7
CFT at baseline (FricTest grade)	3.5 ± 0.8	3.6 ± 0.6	3.4 ± 1.0	3.5 ± 0.8
Duration of SDerm (mo)	55.7 ± 64.7	51.3 ± 46.9	63.3 ± 74.3	53.1 ± 72.3
DLQI score at baseline	11.1 ± 6.1	11.3 ± 5.5	10.6 ± 5.7	11.4 ± 7.3

Data are n (%) for sex, median (interquartile range) for age, or mean ± SD for body mass index, provocation thresholds at baseline, duration of disease, and DLQI score at baseline.

TABLE E2. Reported adverse events

	Patients with SDerm		
Description	**Placebo (n = 21)**	**Omalizumab 150 mg (n = 19)**	**Omalizumab 300 mg (n = 21)**
Total number of adverse events	54	100	57
Total number of serious adverse events	1	1	1
Patients with any adverse event	19 (90)	17 (89)	17 (81)
Patients with any serious adverse event	1* (5)	1† (5)	1‡ (5)
Discontinuation due to adverse event	0	0	0
Adverse events observed in 2 or more patients per treatment group			
Upper respiratory tract infection	8 (39)	12 (63)	6 (29)
Other infections	2 (10)	6 (32)	2 (10)
Headache	10 (48)	6 (32)	9 (43)

Adverse events occurring in 5% or more of patients (ie, more than 2 patients) in the placebo or either omalizumab group are listed separately. Data are n or n (%). Adverse events were classified according to *International Classification of Diseases, Tenth Revision* classifications. A patient who reported 2 or more adverse events within the same organ system was counted only once for that term.

*Renal colic due to calculus of ureter with hospital admission.

†Surgery because of an inguinal hernia.

‡Acute cystitis with hospital admission.

TABLE E3. Comparison of complete responders and partial or nonresponders

Characteristic	Nonresponder or partial responder (n = 19)	Complete responder (n = 18)
Atopy	8 (42%)	7 (39%)
Food allergy	1 (5%)	1 (6%)
CSU comorbidity	1 (5%)	4 (22%)
Presence of other types of CINDU	0 (0%)	1 (6%)
Duration of SDerm (y), mean ± SEM	2.9 ± 0.7	6.8 ± 1.8

Patients were considered positive for "atopy" if there was a positive history of allergic diseases, for example, allergic rhinoconjunctivitis. None of the parameters was statistically significantly different.
CINDU, Chronic inducible urticaria.