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Omalizumab is Effective in Symptomatic Dermographism - results of a Randomized, Placebo Controlled Trial

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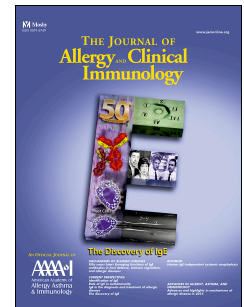
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**Omalizumab is effective in symptomatic dermographism - results of a
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24 **Short summary**

25 We report the results of a randomized controlled multicenter trial in patients with
26 symptomatic dermographism. Treatment with omalizumab 150 mg and 300 mg was
27 effective and well tolerated, as compared to placebo.

28

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 one to two hours.² SDerm commonly lasts for years and significantly impairs quality of life.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 up dosing 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 (CIU), and the drug was licensed for the use in CSU/CIU 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 SDerm patients, in which we evaluated the efficacy and safety of two different doses of omalizumab as compared to placebo.

Overall, 61 SDerm patients were randomized, received at least one treatment, and were included in the safety analyses, and 55 were included in the primary endpoint analysis (For details on study procedures see Suppl. material and Fig E1). The baseline, demographic and clinical characteristics were comparable in all groups (Table E1). Most notably, the mean DLQI score at baseline was 11.1 (Table E1), i.e. a score that indicates a very large effect on quality of life.⁵

Critical friction thresholds (CFT, 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 , $p=0.014$) and 300 mg group ($-2.0 \pm$

0.4, $p=0.004$), as compared to the placebo group (-0.6 ± 0.3 , Fig 1A). Both, omalizumab 150 mg and 300 mg resulted in a rapid improvement of friction thresholds, as early as in week four after the start of treatment (Fig 1B). 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 six weeks after the last treatment. No significant differences between 150 mg and 300 mg omalizumab were observed at any time during the study (Fig 1A, B).

To test if SDerm patients with low and high trigger thresholds and disease activity show differences in their responses to omalizumab, we assessed threshold values in every patient at baseline and ten weeks later. As shown in figure 1C, SDerm patients with low and high baseline thresholds showed similar responses to omalizumab treatment. The rates of SDerm patients who showed complete response at week 10 after placebo treatment were 2/18 (11%), whereas 8/18 (44%) showed complete response to 150 mg omalizumab. With omalizumab 300 mg, 10/19 (53%) showed complete response (Fig 1C). No response at all was observed in 15 of 18 (83%) patients treated with placebo, 6 of 18 (33%) patients treated with omalizumab 150mg, and 8 of 19 (42%) patients treated with omalizumab 300 mg (Fig 1C).

The frequency of adverse events was similar across all groups. The frequency of serious adverse events was low with one event in the 150 mg omalizumab group, one in the 300 mg omalizumab group, and one in the placebo group (Table E2), none of them were considered related to the study medication.

SDerm patients refractory to antihistamine treatment were considerably impaired in their quality of life (QoL, Table E1). Treatment with both, 150 mg and 300 mg omalizumab improved of QoL as assessed by mean Dermatology Life Quality Index (DLQI) scores at week ten compared to baseline (Fig 2A,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 four points in the DLQI scale, the minimal clinically important difference.⁶ In contrast, only 6 of 19 (32%) of placebo treated patients improved by four or more points.

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

Interestingly, both doses of omalizumab, 150 mg and 300 mg, were effective, with no statistical differences between them. This is in contrast to CSU, where 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 non-responders (Table E3), revealed no statistically significant differences between the two 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 if 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 physical urticaria patients.

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

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Keywords

Inducible urticaria, omalizumab, symptomatic urticaria, urticaria factitia, IgE

Figure legends

Figure 1. Omalizumab markedly reduces trigger thresholds in symptomatic dermatographism.

Omalizumab 150mg, omalizumab 300mg, or placebo were injected subcutaneously three times every four weeks and critical friction thresholds (CFT) were assessed using FricTest[®]. Data is presented as **(A)** mean reduction of CTT from baseline at the primary endpoint at week ten and **(B)** mean absolute values at every investigated time point with error bars indicating SEMs. The arrow indicates time of injection, the star indicates the primary endpoint readout two weeks after the last injection. Individual provocation thresholds before and after treatment are shown in **C**.
 *=p<0.05, **=p<0.01, ***=p<0.005, n.s.=not significant.

Figure 2. Omalizumab treatment improves quality of life in patients with antihistamine refractory symptomatic dermatographism.

A. Mean change in DLQI scores assessed at week ten (primary endpoint) to baseline, with error bars indicating SEMs. **B.** DLQI scores assessed at baseline and at ten 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).
 *=p<0.05, **=p<0.01, ***=p<0.005, n.s.=not significant; DLQI=dermatology quality of life index.

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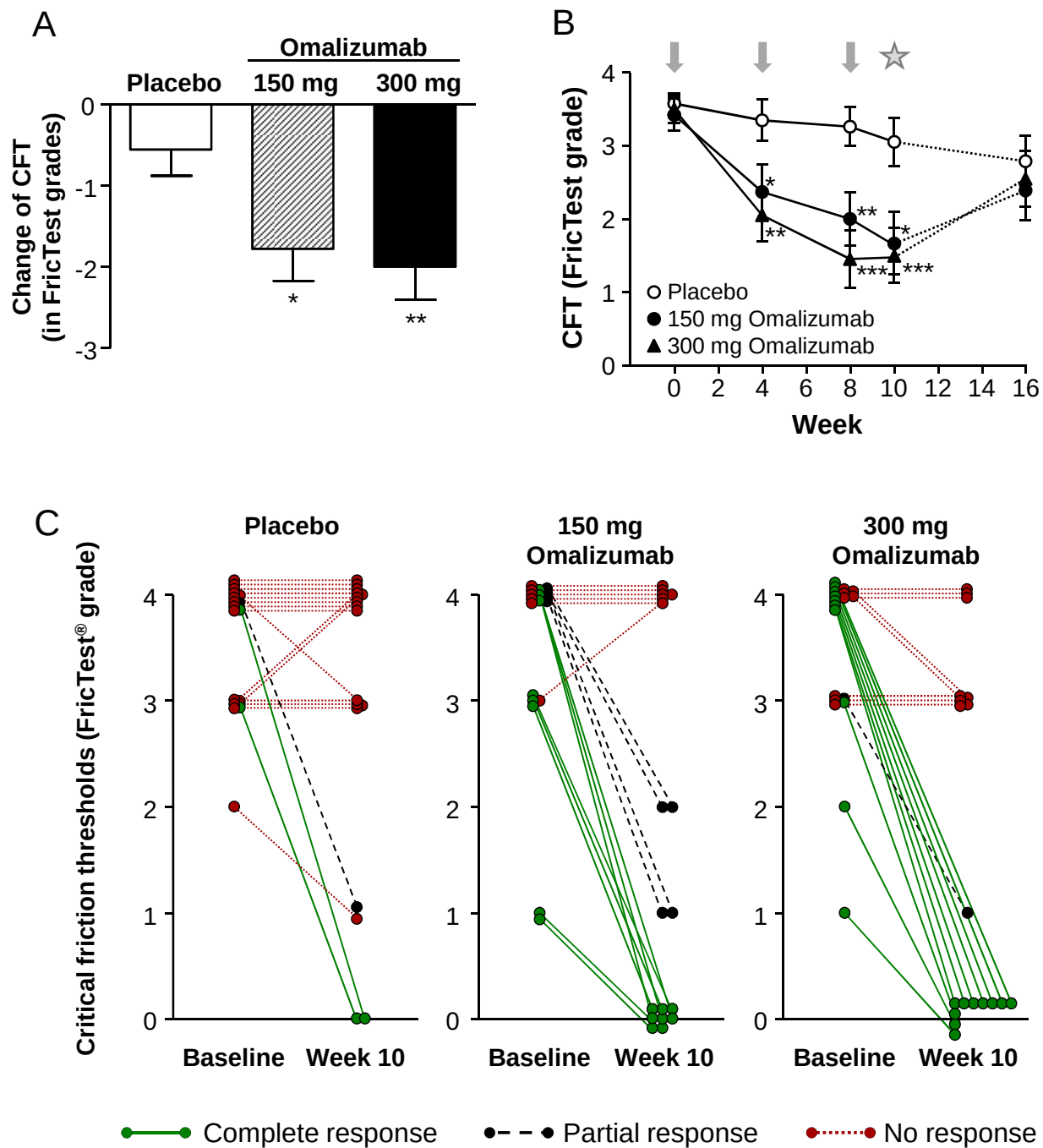


Figure 1

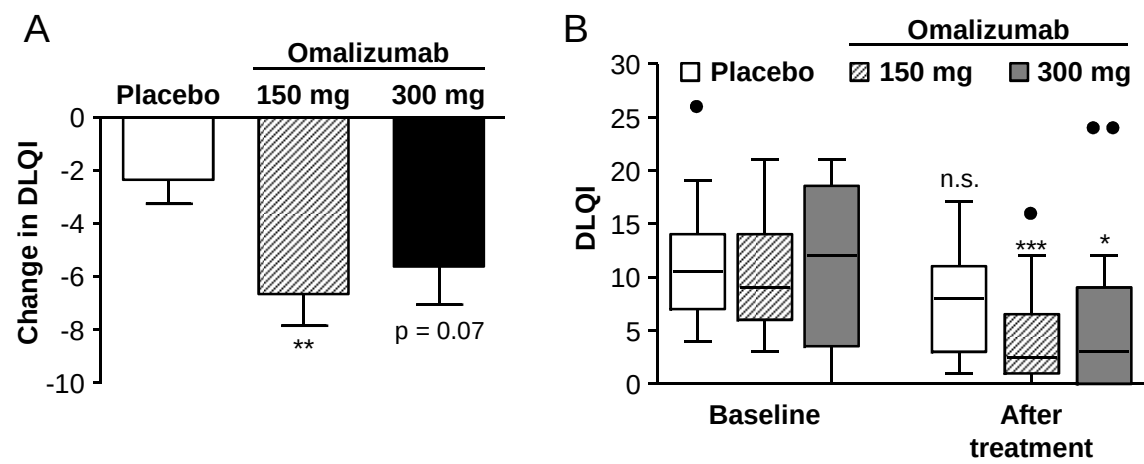


Figure 2

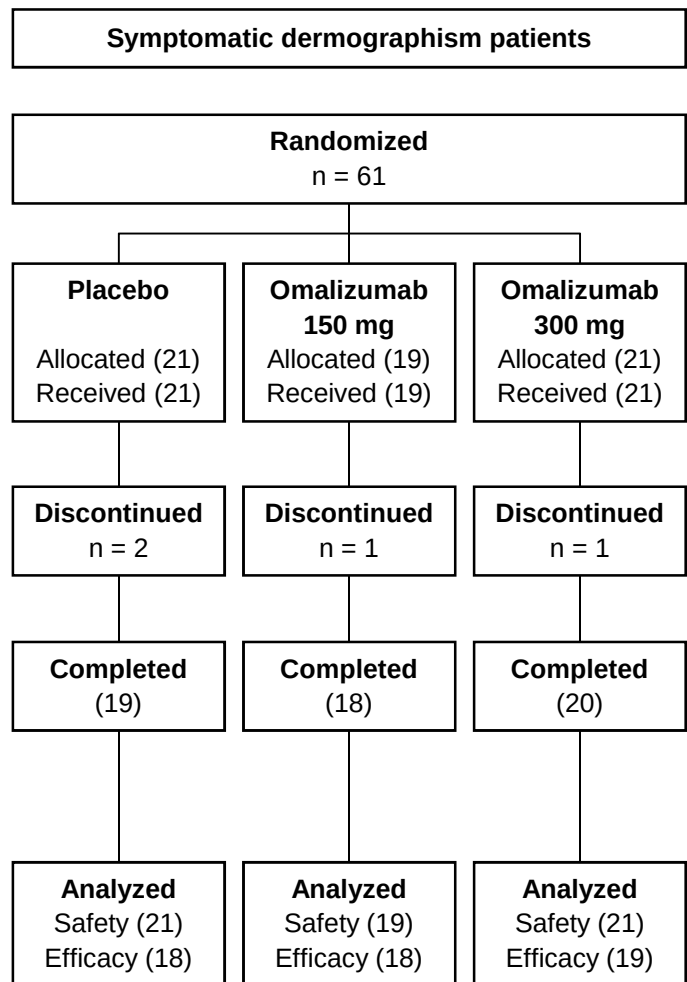


Figure E1

Symptomatic dermatographism patients

	All patients (n=61)	Placebo (n=21)	Omalizumab 150mg (n=19)	Omalizumab 300mg (n=21)
Sex				
Male	27 (44%)	9 (43%)	6 (32%)	12 (57%)
Female	34 (56%)	12 (57%)	13 (68%)	9 (43%)
Age (years)	40 (30-50)	37 (26-46)	45 (34-52)	40 (31-51)
BMI (kg/m²)	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 (months)	55.7 (64.7)	51.3 (46.9)	63.3 (74.3)	53.1 (72.3)
DLQI at Baseline	11.1 (6.1)	11.3 (5.5)	10.6 (5.7)	11.4 (7.3)

Supplementary Table E1

Symptomatic dermographism patients

	Placebo n=21	Omalizumab 150mg; n=19	Omalizumab 300mg; 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* ¹ (5%)	1* ² (5%)	1* ³ (5%)
Discontinuation due to adverse event	0	0	0

*¹ renal colic due to calculus of ureter with hospital admission

*² surgery because of an inguinal hernia

*³ acute cystitis with hospital admission

AEs observed in two 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%)

Supplementary Table E2

	Non 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 (years, mean $\pm$ SEM)	2.9 (0.7)	6.8 (1.8)

Table E3.