

ORIGINAL ARTICLE

Lack of carryover effect on clinical superiority of omalizumab and specific immunotherapy in the subsequent two pollen seasons

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To cite this article: Kopp MV, Hamelmann E, Bendiks M, Zielen S, Kamin W, Bergmann K-C, Klein C, Wahn U. Lack of carryover effect on clinical superiority of omalizumab and specific immunotherapy in the subsequent two pollen seasons. *Pediatr Allergy Immunol* 2013; **00**.

Keywords

omalizumab; specific immunotherapy; seasonal allergic asthma seasonal allergic rhinitis; children

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Accepted for publication 13 May 2013

DOI:10.1111/pai.12098

Abstract

Background: Recently, we showed that combination of omalizumab with specific immunotherapy (SIT) for treatment of patients with seasonal allergic rhinitis (SAR) and comorbid seasonal allergic asthma (SAA) is safe and reduced the symptom load in a statistically significant and clinically meaningful manner during the first pollen season.

Objective: The aim of this study was to investigate long-lasting effects of an initial combination treatment with SIT+omalizumab, a monoclonal anti-IgE antibody, in a follow-up period with SIT treatment only in patients with SAR and comorbid SAA incompletely controlled by conventional pharmacotherapy.

Methods: A randomized, double-blind, placebo-controlled, multicenter trial was performed to assess the efficacy and safety of omalizumab (Xolair[®]) vs. placebo in combination with SIT (depigmented allergoid vaccine, Depigoid[®]) during the first grass pollen season. Omalizumab or placebo therapy was started 2 wk before SIT; the whole treatment lasted 18 wk. After the first pollen season, SIT was given for two subsequent years without omalizumab. Primary end-point was daily 'symptom load', the sum of daily scores for symptom severity and rescue medication use in the second and third year.

Results: A total of 140 patients (age 11–46 yr) were randomized; 130, 128, and 114 patients finished the study after 1, 2, and 3 yr, respectively. The main efficacy variable was the mean daily symptom load as assessed in the patients' diary. No systematic differences between both analysis groups were detected in the findings from symptom load, symptom severity score, or rescue medication score. Further subjective data did not show differences between both groups in the quality-of-life data as assessed with the ACQ, AQLQ, and the RQLQ. Investigators' assessment of treatment effectiveness in the first and second year of study extension showed more patients with favorable long-term treatment outcome ('excellent' and 'good') in the SIT plus omalizumab group than in the SIT plus placebo group. In line with these findings, FEV1 improved at the end of both years in the group which was treated with the combination therapy in the double-blind study compared with the Depigoid plus placebo group.

Conclusion: Eighteen weeks' treatment of omalizumab in combination with SIT in patients with SAR and comorbid SAA reduced the symptom load during the treatment period but showed no prolonged effect during treatment with SIT only. A slight increase in lung function (FEV1) in patients formerly treated with the omalizumab/SIT combination therapy should encourage further evaluation of long-term effects of omalizumab.

The discovery of IgE as a key mediator of airway inflammation in allergic respiratory disease led to the development of anti-IgE antibodies with the aim to interrupt the allergic cascade [1]. Omalizumab, a humanized monoclonal anti-IgE antibody, has been shown to be effective in treating patients with allergic rhinitis and allergic asthma [2–6]. Previously, we have demonstrated that the combination of specific immunotherapy (SIT) plus omalizumab results in a reduction of 39% in symptom load—a score which combines symptom severity and rescue medication use—during the entire pollen season compared with SIT alone [7]. Potentially, these results disclose new perspectives for the application of SIT in patients with moderate-to-severe asthma. Up to now, most clinical trials focused on lack of carryover effect of omalizumab. Therefore, the aim of the follow-up trial was to determine long-lasting effects of an initial 18-wk treatment of SIT plus omalizumab in a follow-up period over two consecutive pollen seasons with SIT treatment only.

Materials and methods

Study design

Details of the study protocol are described in [7]. Briefly, a total of 140 patients were randomized in this multicenter, double-blind, placebo-controlled, parallel-group, multiple-dosing trial comparing (a) omalizumab in combination with depigmented allergoid vaccine (Depigoid®) versus (b) placebo plus depigmented allergoid vaccine (Depigoid®) (randomization scheme 1:1). The depigmented allergoid vaccine (Depigoid®) consisted of depigmented and glutaraldehyde polymerized allergenic extract of 50% grass and 50% rye pollen, adsorbed to aluminum hydroxide. The core study consisted of a 2-wk run-in phase, a pre-seasonal 10-wk treatment phase, and an 8-wk seasonal maintenance treatment phase. During follow-up, all patients were treated with the depigmented allergoid vaccine (Depigoid®) only over the two subsequent years in 4-weekly intervals, but were kept blinded, if they were formerly treated with either omalizumab or placebo. Also, the local study physician, who administered the SIT, was kept blinded over the total study period. On each visit (± 1 wk), 0.5 ml of vial 2 (1000 DPP/ml) was administered. To guarantee for proper safety monitoring, the patient was supervised for at least 30 min after each SIT injection during maintenance treatment in the extension period.

Outcome parameters

Patients were asked to complete a diary to report their symptoms and medication use during the pollen season. The severity of four items—that is, asthma symptoms during day and night, rhinitis, and conjunctivitis—was daily assessed by the patients using a 4-point scale. Symptom severity was derived as the mean of these four ratings (range 0 = no symptoms to 3 = severe symptoms). In addition, use of rescue medication for treatment of asthma and rhinoconjunctivitis was recorded daily during the pollen season in the patient's diary. Symptoms of rhinoconjunctivitis were primarily treated

with systemic antihistamines on an as-needed basis (step 1: levocetirizine 5-mg tablets; 1 point per tablet). If systemic antihistamines did not result in adequate symptom control, the patient received topical nasal steroids after a contact with the study center (step 2: mometasone nasal spray 50 μ g/puff; 3 points per delivery). If no symptom control was achieved, the patient was advised to take an oral corticosteroid (step 3: prednisone 50-mg tablet; 6 points per tablet). Asthma symptoms were initially treated with intermittent short-acting beta-2 agonists (step 1: salbutamol 0.1 mg/puff, 1 point per delivery). If no symptom control was achieved, comedication was increased to low, respectively, medium-dose inhaled corticosteroids (step 2 a: budesonide 200 μ g once daily; 2b: budesonide 200 μ g twice daily; 3 points per delivery) and finally to oral corticosteroids (step 3: prednisone 50-mg tablet; 6 points per tablet). If no symptom control was achieved after step III, the patient had to discontinue with the study. The mean daily symptom load was defined by the sum of the mean daily symptom severity score plus the mean daily rescue medication score.

Secondary efficacy evaluation included global evaluation of treatment effectiveness (GETE), an asthma symptom control scale, quality of life, and lung function parameters (PEF, FEV1). GETE is a 5-point scale assessment of asthma symptom control, which ranges from excellent through good, moderate, and poor effectiveness to worsening in response to asthma treatment [7]. A good or excellent symptom control defines the patient as 'responder'.

Pollen season

The start of the grass pollen season was defined as the first of 3 consecutive days with ≥ 5 grains/m³/24 h. The end of the grass pollen season was defined as the last of 3 consecutive days with ≥ 5 grains/m³/24 h. The rye pollen season is a subset of the grass pollen season defined above. Pollen data were provided for each center in collaboration with the German 'Pollenflugdiens' (pollen counting service, Prof. Bergmann, Berlin). The time interval of the pollen season was determined separately for each center according to the data from its corresponding pollen station.

Study population

The study was conducted with female and male patients with seasonal allergic asthma (SAA; not adequately controlled in previous seasons before entering the double-blind study period) and seasonal allergic rhinoconjunctivitis (SAR), with a total IgE level 30–700 IU/ml, age 12–45 yr, with documented evidence of specific serum IgE and clinically relevant symptoms caused by allergy to grass or rye pollen. Patients who had finished the core study ($n = 130$) continued SIT monotherapy in the extension periods, consistent with the recommendation of 3 consecutive years of immunotherapy by current treatment guidelines (Fig. 1).

The study design was approved by the ethics committees of the participating centers in Germany, announced to the authorities, and registered in the EUDRACT study database (2005-003860-47).

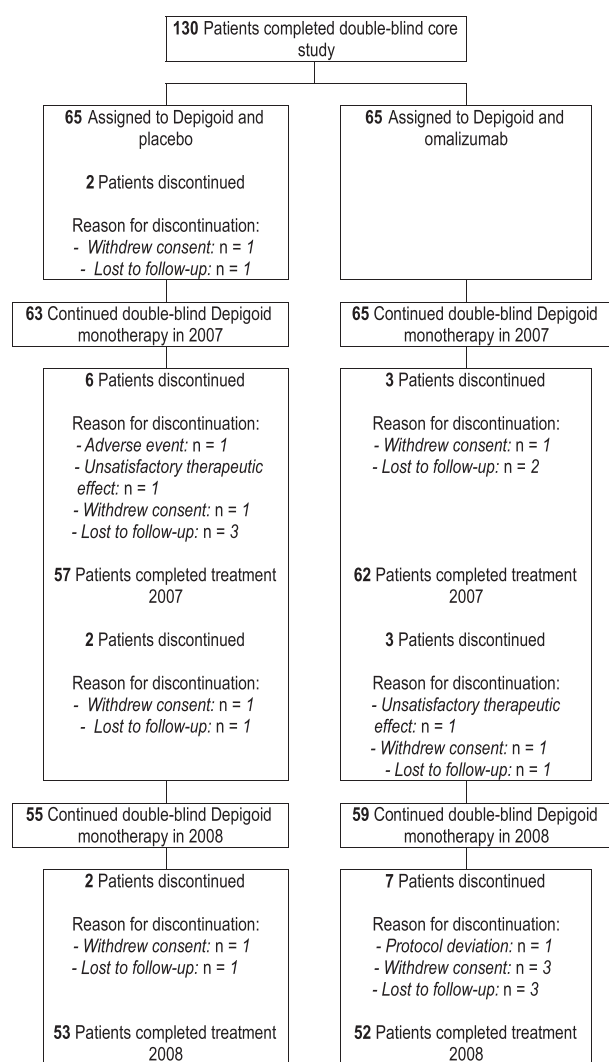


Figure 1 Trial flow diagram.

Results

A total number of 128 (2007) and 114 (2008) patients, respectively, continued treatment with depigmented allergoid vaccine (Depigoid®) within the extension phase of this study. A number of 105 patients (80.8%) completed the 2-year extension phase (Fig. 1). The retention rate in this long-term trial is high although the study requested from the patients to complete a patient diary during the pollen season. Slightly more men than women participated in the present trial; all participants but one were Caucasians. About 10–12% of the patients were current smokers (Table 1).

The main efficacy measure was the mean daily symptom load, which combined symptom severity and rescue medication score. No statistically significant difference between the former omalizumab group and the former placebo group was observed (2007: SIT + omalizumab 1.25 versus SIT + placebo 1.1; 2008: 1.32 versus 0.97; Fig. 2). The symptom load during the core

study was 0.49 in the SIT and omalizumab group compared with 0.8 in the SIT and placebo group ($p = 0.04$).

The symptom severity score yielded nearly identical mean values for both treatment groups during the 2007 and 2008 extension season (Wilcoxon 2007: $p = 0.964$, Wilcoxon 2008: $p = 0.81$). The results from rescue medication score were also similar in both extension seasons with a slightly higher rescue medication score in the former omalizumab group compared with placebo, but the group difference was at random in both seasons (Wilcoxon 2007: $p = 0.275$, Wilcoxon 2008: $p = 0.451$) (Table 2).

Throughout both seasons and across treatment groups, for the majority of the patients, no clinical change was reported in the asthma control and quality-of-life questionnaires (AQLQ), the rhinitis control and quality-of-life questionnaires (RQLQ), and work productivity and activity impairment questionnaire (WPAI-AA) (data not shown).

The global evaluation of treatment effectiveness (GETE) by investigator and patients was slightly in favor of patients treated with omalizumab and SIT during the first year. However, the differences were only statistically significant in the second extension season 2008 but not in 2007. 77.8% and 72.7% of the investigators assessed the treatment efficacy in the former omalizumab and SIT group as excellent or good compared with 64.3% and 46.3% in the former SIT and placebo group (2007: $p = 0.11$; 2008: $p = 0.006$, two-sided Fisher's exact test) (Fig. 3a,b). During both seasons, no remarkable differences in the patients' ratings were observed: 66.1% and 63.7% of the patients ranked the treatment efficacy in the former omalizumab and SIT group as excellent or good compared with 60% and 51% in the former SIT group (Fig. 3c,d).

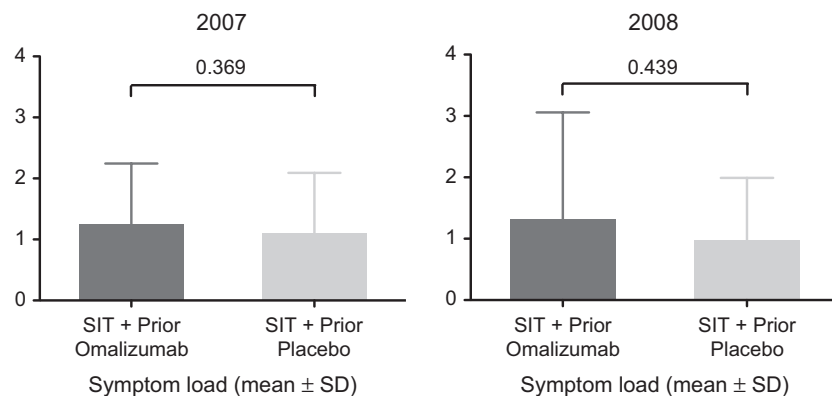
In addition to clinical parameters, effects on lung function were assessed. The ANCOVA was calculated using baseline as covariate for both FEV1 and PEF. With the ANCOVA, group differences in FEV1 (% derived) favoring omalizumab treatment were found at the end of the first (mean difference 2.9; 95% CI: -0.5 – 6.2 ; $p = 0.09$) and second year (mean difference 3.9; 95% CI: -0.2 – 7.6 ; $p = 0.038$) of the extension period. For PEF measurements, no significant group differences arose from ANCOVA during both seasons (2007: mean difference 13.9; 95% CI: -7.4 – 35.2 ; $p = 0.19$; 2008: mean difference 8.1; 95% CI: -15 – 31.1 ; $p = 0.49$).

The mean intensity of the grass pollen seasons, measured in number of grains/m³/24 h, was comparable during the three seasons: In 2006, mean intensity was 32.3; in 2007: 31.7, and in 2008: 29.2 grains/m³/24 h.

We observed no systemic reactions to the study drug at any time point. During the first year, approximately half of the patients in each treatment group were affected by at least one adverse event. Patients in the SIT + omalizumab group showed a statistically non-significant trend of less local side effects after the injections compared with the SIT + placebo group (7). Adverse events during the extension period, which were suspected to be related to depigmented allergoid vaccine (Depigoid®), were in most cases reactions at the injection site in both treatment groups during either seasons (2007: SIT + omalizumab 16.9% versus SIT + placebo 15.9%; 2008:

Table 1 Demographic data during extension period

	2007		2008	
	Depigoid + Omalizumab (N = 65)	Depigoid + Placebo (N = 63)	Depigoid + Omalizumab (N = 59)	Depigoid + Placebo (N = 55)
Age (yr)				
Mean $\pm$ s.d.	27.8 $\pm$ 9.9	30.4 $\pm$ 10.6	27.6 $\pm$ 9.9	30.1 $\pm$ 10.9
Median (range)	29.0 (11–46)	33.0 (12–45)	29.0 (11–46)	32.0 (12–45)
Age groups – n (%)				
<12 yr	1 (1.5)	–	1 (1.7)	–
12–18 yr	14 (21.5)	15 (23.6)	13 (22.0)	15 (27.3)
>19–29 yr	18 (27.7)	10 (15.9)	16 (27.1)	8 (14.5)
≥ 30 yr	32 (49.2)	38 (60.3)	29 (49.2)	32 (58.2)
Sex – n (%)				
Male	37 (56.9)	36 (57.1)	35 (59.3)	29 (52.7)
Female	28 (43.1)	27 (42.9)	24 (40.7)	26 (47.3)
Race – n (%)				
Caucasian	65 (100)	62 (98.4)	59 (100)	54 (98.2)
Asian	–	1 (1.6)	–	1 (1.8)
Smoker – n (%)				
No	57 (87.7)	56 (88.9)	53 (89.8)	49 (89.1)
Yes	8 (12.3)	7 (11.1)	6 (10.2)	6 (10.9)
Smoker (packyear)				
Mean $\pm$ s.d.	2.8 $\pm$ 2.43	1.9 $\pm$ 0.90	3.3 $\pm$ 2.58	1.7 $\pm$ 0.82
Median (range)	1.5 (1–7)	2.0 (1–3)	2.5 (1–7)	1.5 (1–3)

**Figure 2** Symptom load in the former omalizumab group [depigmented allergoid vaccine (Depigoid®) + omalizumab] and the former placebo group [depigmented allergoid vaccine (Depigoid®) + placebo] in the first season (2006) and both extension seasons (2007 and 2008). No significant differences were observed between both groups.**Table 2** Summary of ANOVA on symptom severity and rescue medication score during the core study 2006 and in both extension seasons 2007 and 2008. The group difference was tested with the Wilcoxon test

	2006 (Core study)		2007 (Extension)		2008 (Extension)	
	SIT & Omalizumab	SIT & Placebo	SIT & former Omalizumab	SIT & former Placebo	SIT & former Omalizumab	SIT & former Placebo
Symptom severity	0.38	0.59	0.55 $\pm$ 0.4	0.55 $\pm$ 0.38	0.54 $\pm$ 0.42	0.5 $\pm$ 0.37
	p = 0.016		p = 0.9		p = 0.81	
Rescue Medication Score	0.38	0.38	0.7 $\pm$ 0.8	0.55 $\pm$ 0.8	0.78 $\pm$ 1.6	0.47 $\pm$ 0.97
	p = 0.29		p = 0.275		p = 0.451	

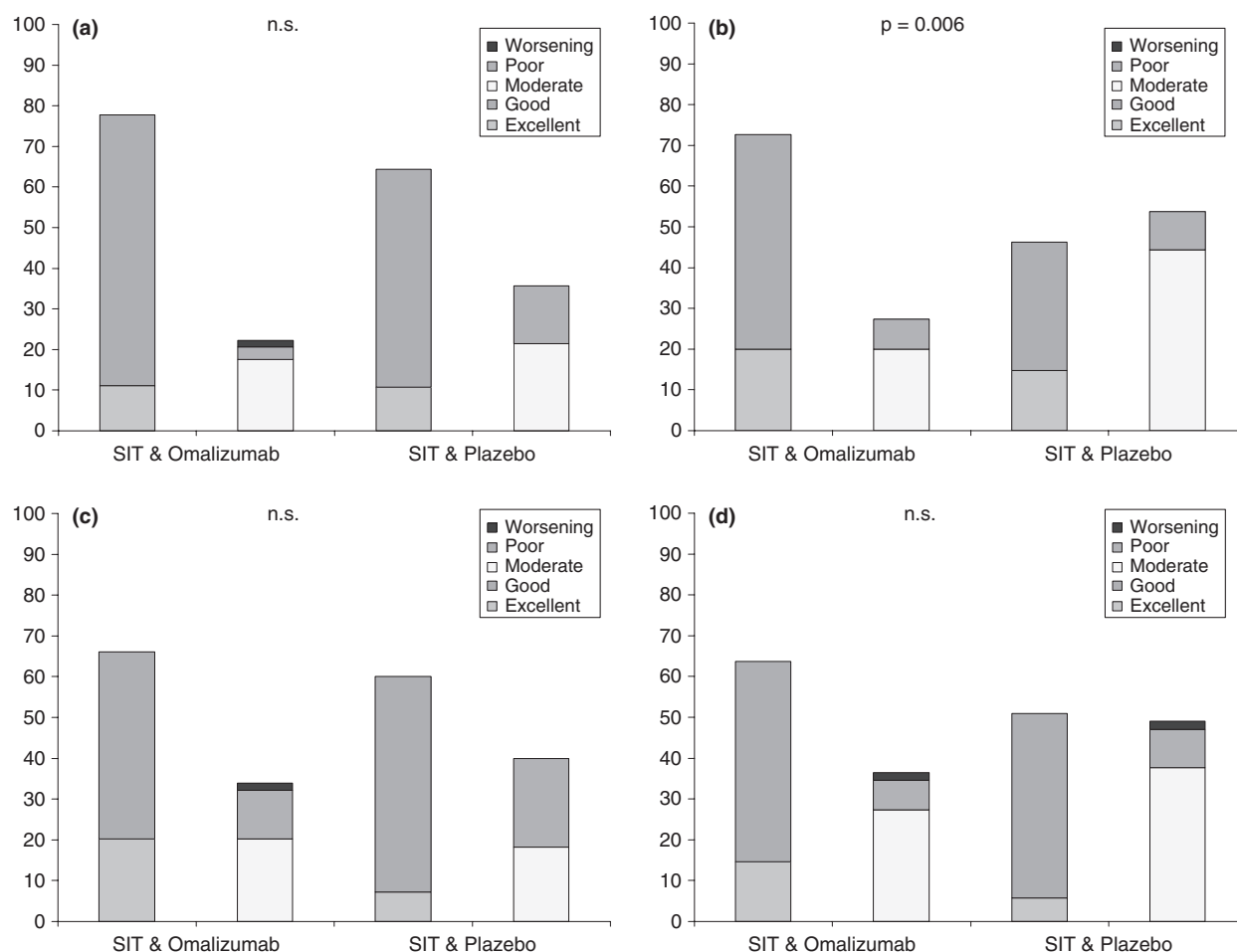


Figure 3 Global evaluation of treatment effectiveness (GETE) by investigator in the extension season 2007(3a) and 2008(3b) and GETE by patient in the extension season 2007(3c) and 2008(3d) in the former omalizumab group (SIT + omalizumab) and the former placebo group (SIT + placebo). Values indicate percentage of patients. A two-sided Fisher's exact test was performed to test statistically significant differences between the groups.

8.5% versus 14.5%). The most frequently occurring adverse events were infections (2007: 53.8% versus 44.4%; 2008: 49.2% versus 47.3%) as well as respiratory, thoracic, and mediastinal disorders, including asthma, cough, and allergic rhinitis symptoms (2008: 21.5% versus 25.4%; 2008: 16.9% versus 20%). This observation was categorized as 'not related to study medication' and applied equally on both treatment groups throughout the extension phase.

Discussion

Results of clinical trials in patients with rhinitis and asthma have shown that combination of omalizumab plus SIT may be beneficial for the treatment of allergic diseases by improving symptoms and limiting side effects [8, 9]. However, most of these trials covered only a relatively short observation period.

Recently, we demonstrated that combination of omalizumab with SIT significantly reduced the symptom load compared with those on SIT alone in patients with seasonal allergic

rhinitis (SAR) and comorbid seasonal allergic asthma (SAA) [7]. This follow-up study investigated the long-lasting effects of omalizumab (pre- and co-) treatment in combination with SIT in patients with SAR and comorbid SAA incompletely controlled by conventional pharmacotherapy. Depigmented allergoid vaccine (Depigoid®) monotherapy over two consecutive years (2007 and 2008) was efficacious and safe, irrespective of the former 18-wk treatment with omalizumab or placebo. Former treatment with omalizumab for 18 wk showed no difference after the one- and two-year follow-up in terms of symptom load, symptom severity, and rescue medication use but showed significant improvement in lung function and GETE responder evaluation by the investigator at the end of the study. However, long-term follow-up of the initial two treatment groups during open-label depigmented allergoid vaccine (Depigoid®) monotherapy did not show differences between the groups in the patients' assessment of disease-specific symptoms and related consequences on quality of life and activities of daily living.

According to the objective measures of the lung function (FEV1) and the investigators' assessment of treatment effectiveness, the initial combination treatment with depigmented allergoid vaccine (Depigoid®) and omalizumab showed a more favorable clinical long-term outcome in both years of the extension phase. It may be speculated that the investigators' ratings depend to some extent on the measures of the lung function. This hypothesis is confirmed by the small but noteworthy correlation that was found between the FEV1 values and the investigators' GETE ratings for both seasons (Pearson correlation first year: $r = -0.2349$ with $p = 0.0104$; second year: $r = -0.1673$ with $p = 0.0820$). Moreover, the global assessments of treatment efficacy by the physician might be also influenced by memory of the superior results in the first year when the patients received omalizumab. Finally, the effect size of these results is small, the difference was limited to one parameter (FEV1, but not PEF), and statistical significance was only observed in the second year of study extension. Therefore, conclusions about disease-modifying aspects of omalizumab treatment should be drawn with caution. The small effects on lung function and GETE must be weighted against cost-effectiveness and clinical aspects. In general, omalizumab is approved by the European Union in 2009 for children >6 yr of age and adults with severe allergic asthma, uncontrolled despite oral steroids or high doses of inhaled steroids combined with long-lasting beta-agonists and antileukotrienes. For the majority of patients who tolerate SIT therapy without significant side effects, the presented data do not encourage the use of omalizumab as a standard add-on therapy to SIT. However, patients with severe side effects during SIT hampering regular dose escalation might profit by pre-treatment with omalizumab. Moreover, in selected patients with partially uncontrolled asthma, the combination of omalizumab and SIT may provide improved safety in addition to superior symptom relief when compared with SIT alone. Up to now, there are no data available if the clinically useful approach of pre-treatment is also cost-effective.

The significance of long-term effectiveness of omalizumab treatment on allergic diseases is a key unanswered question [10]. There is some evidence from a small group of cat and mite allergic asthmatic patients, who received omalizumab treatment over 6 yr. In total, 13 of 18 patients had improved or remained stable after cessation of omalizumab over an additional observation period of up to 3 yr. The authors speculate that these results might be explained by downregulation of basophil and presumably also mast cell IgE receptors and thus reactivity [11, 12].

Indirect evidence of a potential long-term impact also arises from the observation that effectiveness of omalizumab can be maintained in allergic diseases even if the initial 2- or 4-wk dosing regime was extended over time [13].

Recently, Lowe and Renard aimed to determine whether IgE production remains constant over time or decreases with omalizumab treatment. Data from seven clinical trials were used for a model-based pharmacokinetic-pharmacodynamic analysis of omalizumab, free and total IgE, indicating that omalizumab reduced IgE production over time. They calculated

an estimated rate of about 54% decrease in IgE production per year, indicating that it would take 3–5 yr to achieve a new steady state in omalizumab responders [14]. Of note, IgE production paralleled the decline in total IgE serum levels, raising the feasibility to use total IgE as a measure of monitoring IgE production and guiding individual treatment decisions in patients under omalizumab.

Omalizumab can be considered to be safe in children and adults with allergic diseases [15, 16]. Adverse events that were suspected to be related to depigmented allergoid vaccine (Depigoid®) in our trial were in most cases reactions at the injection site in both treatment groups during either season. The most frequently occurring adverse events were infections as well as respiratory, thoracic, and mediastinal disorders. This observation applied equally on both treatment groups throughout the complete extension phase and was categorized as 'not related to study medication'.

In summary, there are a number of intriguing immunologic and clinical observations that omalizumab might also exhibit long-lasting effects. However, these effects possibly will only be obvious after a treatment period of about 5–6 yr. We failed to detect differences between patients treated with omalizumab and specific immunotherapy in comparison with specific immunotherapy and placebo with respect to symptom load or quality of life in the extension phase of our study after discontinuation of omalizumab treatment. This might be explained by the relatively short intervention phase with only 18 wk of treatment with omalizumab. Moreover, the absence of a pure placebo group and the fact that both groups received a relevant anti-allergic therapy might conceal a potential omalizumab effect. Finally, this trial was not powered to detect disease-modifying effects of omalizumab.

A slight increase in lung function in patients formerly treated with the omalizumab/SIT combination therapy should encourage further evaluation of long-term effects of omalizumab. Until then, allergen-specific immunotherapy is the only therapeutic option that has the potential to restore tolerance and to modify the disease course by preventing new allergic sensitization and/or the progression from allergic rhinitis to asthma [17].

Acknowledgments

The authors thank all participating investigators of the DUAL (Depigoid und OmalizUmab bei Asthma Saisonale) study: M.V. Kopp, U. Luetke Volksbeck, R. Grychtol, and J. Lange (Freiburg), E. Hamelmann (Bochum), U. Wahn, P. Stock, and K. Parasher (Berlin), K.-C. Bergmann, M. Worm, and L. Hae-Hyuk (Berlin), S. Zielen and J. Schulze (Frankfurt/ Main), U. Schauer and T. Rothoef (Bochum), W. Kamin, G. Sahin, and B. Klaer-Hlawatsch (Mainz), R. Brehler and P. Hemfort (Muenster), K.-M. Beeh and J. Beier (Wiesbaden), G. Kunkel, D. Herold, and J. Kleine-Tebbe (Berlin), J.C. Virchow, A. Bier, and P. Stoll (Rostock), K.-O. Steinmetz and U. Lessing (Darmstadt), O. Kornmann and A. Eich (Mainz), R. Deckelmann and G. Eckardt (Leipzig), L. Klimek and O. Pfaar (Wiesbaden), L. Lindemann, S. Wild, and G. Ern (Gelsenkirchen), W. Feussner and A. Debertin (Kassel), N. Peslis

(Eschwege), R. Balzer (Gummersbach), W. Ziegler, and D. Wehrmann (Freudenberg) and L. Volgmann (Hannover).

The authors thank G. Petry (Seligenstadt), S. Di Silvestro (Frankfurt), J. Felgner (Leipzig), C. Frahm (Berlin), J. Grefer (Haan), P. Jaeger (Freiburg), J. Jahr, and A. Bissert (Nuernberg), H. Kampmann (Blankenheim), N. Kotzor (Veitsbronn), L. Magdaleno-Maiza (Frechen), Target-Team (Engelskirchen),

and U. Zacharias (Kogel) who were responsible for monitoring and logistics.

The authors also thank Sandra Schreiber for critically reading the manuscript.

The study was supported by a grant from Novartis Pharma GmbH, Nuernberg.

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