

ORIGINAL PAPER

Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma

M. V. Kopp*, E. Hamelmann†, S. Seyfried‡, S. Zielen§, W. Kamin¶, K.-C. Bergmann||, C. Sieder‡, S. Stenglein‡ and U. Wahn** for the DUAL study group

*Zentrum für Kinder- und Jugendmedizin, University of Freiburg, Freiburg, Germany, †Kinderklinik St Joseph Hospital, Ruhr-University of Bochum, Bochum, Germany,

‡Novartis Pharma GmbH, Nuernberg, Germany, §Klinik für Kinderheilkunde, University of Frankfurt, Frankfurt, Germany, ¶Kinderklinik der Johannes

Gutenberg-Universität Mainz, Mainz, Germany, ||Allergie-Zentrum-Charité, Berlin, Germany and **Charité Virchow-Klinikum, Humboldt-University, Berlin, Germany

Clinical and Experimental Allergy

Summary

Background The treatment of allergic asthma by specific immunotherapy (SIT) is hampered by potential side-effects.

Objective The aim of this study was to study the effect of omalizumab, a monoclonal anti-IgE antibody, in combination with SIT in patients with seasonal allergic rhinoconjunctivitis (SAR) and co-morbid seasonal allergic asthma (SAA) incompletely controlled by conventional pharmacotherapy.

Methods A randomized, double-blind, placebo-controlled, multi-centre trial was performed to assess the efficacy and safety of omalizumab (Xolair®) vs. placebo in combination with depigmented SIT (Depigoid®) during the grass pollen season. Omalizumab or placebo was started 2 weeks before SIT; the whole treatment lasted 18 weeks. Primary endpoint was daily 'symptom load', the sum of daily scores for symptom severity and rescue medication use.

Results A total of 140 patients (age 11–46 years) were randomized; and a total of 130 finished the study. Combination therapy reduced the symptom load by 39% ($P = 0.0464$, Wilcoxon test) over SIT monotherapy. This difference was mainly due to reduced symptom severity ($P = 0.0044$), while rescue medication use did not change significantly. Combination therapy also improved asthma control (Asthma Control Questionnaire, $P = 0.0295$) and quality of life in the case of asthma (Asthma Quality of Life Questionnaire, $P = 0.0293$) and rhinoconjunctivitis (Rhinoconjunctivitis Quality of Life Questionnaire, $P = 0.0537$). Numbers of patients with 'excellent or good' treatment efficacy according to ratings of investigators (75.0% vs. 36.9%) or patients (78.5% vs. 46.1%) were markedly higher in the combination group than under SIT alone.

Conclusion Combination of omalizumab with SIT for treatment of patients with SAR and co-morbid SAA was safe and reduced the symptom load in a statistically significant and clinically meaningful manner.

Keywords children, omalizumab, seasonal allergic asthma, seasonal allergic rhinitis, specific immunotherapy

Submitted 7 July 2008; revised 20 August 2008; accepted 5 September 2008

Correspondence:

Prof. Dr Matthias Volkmar Kopp,
Zentrum für Kinder- und
Jugendmedizin, University Freiburg,
Mathildenstrasse 1, 79106 Freiburg,
Germany. E-mail:
matthias.kopp@uniklinik-freiburg.de

Introduction

Allergic diseases such as seasonal allergic rhinoconjunctivitis (SAR) and seasonal allergic asthma (SAA) frequently coexist in the same patients [1]. Prospective studies suggest that SAR might be a predisposing risk

factor for developing asthma. Moreover, many patients with rhinitis alone demonstrate non-specific bronchial hyperresponsiveness and airway inflammation comparable with subjects with clinical asthma [2, 3]. Furthermore, the physical condition of co-morbid patients at peak pollen season is significantly worse compared with

patients with SAR alone, and an impairment of quality of life is incremental if co-morbid patients are compared with patients with either asthma or rhinitis [4, 5].

For patients demonstrating a clear relationship between allergic sensitization and disease, specific immunotherapy (SIT) is indicated as the only specific and causal treatment [6]. Moreover, subcutaneous immunotherapy is the only treatment with documented long-term efficacy after termination [7, 8]. Unfortunately, SIT is to some extent burdened with the risk of inducing systemic side-effects, particularly for patients with SAA [9, 10]. Recently, we have shown that the combination of 'active immunization' with standardized allergen extracts (SIT) and treatment with anti-IgE antibody (omalizumab) was superior to using SIT alone in terms of reducing symptoms and the use of rescue medication in children with grass and birch-pollen SAR throughout the pollen season [11]. The attraction of the combined therapy is a complementary mode of action: while application of specific allergen during SIT induces regulatory immune elements and specific tolerance [12], omalizumab reduces allergen-induced responses by decreasing levels of free serum IgE [13], expression of high-affinity IgE receptors [14] and mediator release of the immediate-type hypersensitivity reaction such as histamine and leukotrienes [15, 16]. This mechanism best explains why pre-treatment with omalizumab, before an intensified rush immunotherapy, compared with SIT alone significantly decreased allergic side-effects, including anaphylaxis reactions, in patients with ragweed-induced SAR [17]. It was therefore tempting to speculate that application of omalizumab in combination with SIT may also provide faster symptom relief and better safety compared with SIT alone in patients with complex and symptomatic allergic disease, i.e. co-morbid SAR together with SAA. For both diagnoses, the efficacy of humanized monoclonal anti-IgE, omalizumab (Xolair[®]) has already been demonstrated. Significant clinical improvements were shown as regards symptom severity, lung function, medication use and quality of life in a series of further studies [11, 17, 18–20].

The aim of this study was to evaluate the efficacy, safety and quality of life of omalizumab in combination with a SIT with depigmented grass pollen allergoid compared with SIT plus placebo. Therefore, we enrolled a population of adults and adolescents (age 12–45 years) with SAR and mild SAA sensitized against grass pollen allergens.

Materials and methods

Study design

A total of 140 patients [intention-to-treat population (ITT)] were randomized in this multi-centre, double-blind, placebo-controlled, parallel-group, multiple-dose trial comparing (a) omalizumab (Novartis, Europharm Limited,

Horsham, UK) in combination with Depigoid (Leti Pharma GmbH, Witten, Germany) vs. (b) placebo in combination with Depigoid (randomization scheme 1 : 1). A total of 130 patients finished the study [per-protocol population (PP)]. The core study consisted of a 2-week run-in phase, a pre-seasonal 10-week treatment phase and an 8-week seasonal maintenance treatment phase with double-blind administration of omalizumab or placebo in both treatment phases. Randomization numbers were generated using a validated system that automates the random assignment of treatment arms to randomization numbers.

Omalizumab or placebo was started 10 weeks before the expected pollen season and 2 weeks before SIT and ended after 18 weeks in total. Depigoid was administered open-labelled and started 8 weeks before the expected pollen season. A pre-seasonal rush titration protocol was chosen for Depigoid, as recently described [21]. Patients received a therapeutic vaccine containing depigmented and glutaraldehyde-modified grass pollen extract. The schedule of administration involved injecting 0.2 and 0.3 mL of the vial of maximum concentration during the first day of immunotherapy, separated by a time interval of 30 min. After rush titration, the patients were maintained at a dose of 0.5 mL every 4 weeks. Written informed consent was obtained from all patients. In case of patients less than 18 years old, written informed consent was obtained from children's parents.

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

Patients

The study population (for demographic characteristics, see Table 1) was defined as patients with a total IgE level ≥ 30 – ≤ 700 IU/mL and a diagnosis of not adequately controlled mild to moderate seasonal grass pollen (or rye pollen or both) allergic rhinoconjunctivitis with concomitant seasonal asthma. Patients had to demonstrate a positive specific IgE for grass/rye pollen at screening (≥ 0.7 U/L; ImmunoCAP, Phadia, Uppsala, Sweden), or within the previous 12 months. Seasonal asthma was considered not adequately controlled if the patient described having had bothersome symptoms of seasonal asthma within ≥ 2 previous seasons but normal lung function testing [forced expiratory volume in 1 s (FEV₁) $\geq 80\%$ of the predicted normal value for the patient] outside the pollen season at screening. Patients with a total IgE < 30 or > 700 IU/mL, with severe persistent allergic asthma, with significant clinical manifestations of allergy as a result of sensitization against other inhalant allergens (tree or weed pollen, house dust mite or animal dander), with a smoking history > 10 pack years, with an active lung disease other than allergic asthma (e.g.

chronic bronchitis, COPD) or patients with significant acute or chronic underlying medical conditions were excluded.

Definition of the pollen season and a pollen day

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

Treatment

The omalizumab dose to be administered was based on the patient's body weight and total serum IgE level at the screening visit and was applied either at 2-week or at 4-week intervals. The number of injections and injection volume was determined from dosing tables. Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site. To guarantee proper safety monitoring, the patients were supervised 1 h after each injection of omalizumab. Two weeks after omalizumab or placebo treatment, all patients received additionally Depigoid s.c. for 16 weeks. They started with initial rush-immunotherapy build-up phase and were maintained at a dose of 0.5 mL every 4 weeks. The used extract of Depigoid consists of depigmented and glutaraldehyde-polymerized allergenic extract of grass and rye pollen adsorbed onto aluminium hydroxide. The extract contains the species *Phleum pratense*, *Lolium perenne*, *Dactylis glomerata*, *Poa pratensis* and *Festuca elatior* in equal proportions.

Detailed prescriptions of rescue medications for asthma and rhinoconjunctivitis were provided in the study protocol. Symptoms of rhinoconjunctivitis were allowed to be treated at first with systemic antihistamines on an as-needed basis (step 1: levoceterizine 5 mg tablets; one point per tablet). If systemic antihistamines as initial rescue medication did not result in adequate symptom control, the patient was advised to contact the study centre where the following escalation comedication was provided (step 2: mometasone nasal spray 50 µg/puff; three points per delivery). If no symptom control was achieved, the patient received an oral corticosteroid (step 3: prednisone 50 mg tablet; six points per tablet). For asthma, symptoms of bronchospasm were initially treated with intermittent short-acting beta-2 agonists (step 1: salbutamol 0.1 mg/puff, one point per delivery). If no symptom control was

achieved, rescue medication was increased to low or medium-dose inhaled corticosteroids (step 2a: budesonide 200 µg once daily; 2b: budesonide 200 µg twice daily; three points per delivery) and finally to oral corticosteroids (step 3: prednisone 50 mg tablet). If no symptom control was achieved after step 3, the patient had to discontinue with the study. Use of rescue medication was recorded daily after start of study drug in the patient's diary.

Outcome parameters

Patients were asked to complete a diary between the screening visit and the last visit in the study. Using a four-point scale, the severity of four items – i.e. asthma symptoms during the day and the night, rhinitis and conjunctivitis – was assessed by the patients. Symptom severity was derived as the mean of these four ratings (range 0 = no symptoms to 3 = severe symptoms). In addition, a rescue medication score for treatment of asthma and rhinoconjunctivitis was defined as the mean of the daily rescue medication scores during the pollen season. Weights are given as point values to medications as indicated above.

In accordance with previous trials, the mean daily symptom load was defined as the sum of the mean daily symptom severity score and the mean daily rescue medication score [11]. Secondary efficacy evaluation was based upon the best morning peak expiratory flow rate (PEF), global evaluation of treatment effectiveness (GETE), an asthma symptom control scale, quality of life and spirometry.

GETE is a five-point scale assessment of asthma symptoms control, which ranges from excellent through good, moderate and poor effectiveness to worsening in response to asthma treatment [22]. A good or excellent symptom control defines the patient as 'responder'. The evaluation was performed independently at the end of the study, at first by the patient, and then, after interview and physical examination, by the investigator. Additionally, asthma symptoms were evaluated using the Asthma Control Questionnaire (ACQ) [23]. The influence of study treatment on quality of life was investigated with the disease-specific Asthma Quality of Life Questionnaire (AQLQ) [24] and the Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [25]. Pulmonary function was also monitored by spirometry assessment.

Tolerability was evaluated by means of an analysis of adverse events. Safety was assessed by observing clinically notable changes in haematology, blood chemistry and urine variables, and by evaluating vital signs.

Statistical analysis

The primary objective of this study was to demonstrate that depigmented SIT therapy in combination with

omalizumab had superior efficacy compared with depigmented SIT monotherapy for daily symptom load averaged over the pollen season of the core study. The sample-size calculation before the study was based on the assumption that the absolute levels of the symptom load as well as their standard deviation will depend on the length and the strength of the next pollen season, which is unknown at the time of trial planning. We calculated that 70 patients/group will result in 86% power on a two-sided, 5% significance level to detect a difference between treatment groups if the true difference is at least moderate, i.e. exceeds 50% of the standard deviation. Prior experience suggests that omalizumab will achieve this level of superiority, even if one accounts for a drop-out rate of 10% [11].

The primary analysis was performed in the ITT population comparing treatments with an ANOVA model with the factors treatment and centre. Although the distribution of the primary endpoint was skewed and deviated from normality, a parametric model was preferred for the analysis. A recent publication has demonstrated that parametric models perform quite well under such circumstances, whereas non-parametric tests which do not assume normality are rather vulnerable to variance heterogeneities often associated with skewed distributions [26]. Applying a logarithmic transformation ($y = \log(y+1)$), skewness of data was removed. Centre was included because the definition of the characteristics of the pollen season (duration and strength) was based on centre. Treatment groups were also compared with a non-parametric Wilcoxon test.

Secondary medication and symptom scores and quality of life were analysed in the same way as the primary endpoint. For lung function parameters (FEV₁% and PEF), baseline values were also used as covariates. GETE was analysed using Mantel-Haenszel χ^2 -test or Fisher's exact test. All analyses on secondary efficacy data are interpreted in an exploratory manner. All efficacy analyses were performed with ITT and PP population. The ITT population was defined as being all randomized and treated patients for whom at least one efficacy assessment was available during the pollen season. From the PP population, patients with major protocol violations were excluded. Safety and tolerability were analysed in all patients who had received at least one dose of omalizumab, depigmented SIT or placebo.

Results

Patients

A number of 140 patients, 70 in each treatment group, were treated in 20 centres in Germany. Disposition of all enrolled patients and analysis populations is reported in Fig. 1. Demographic data and clinical characteristics of

the study population are shown in Table 1. Pollen counts were determined from 10 pollen counting stations in Germany. Patient diaries with symptom assessments on pollen days were available for a median number of 60 days (range 1–76 days) in the omalizumab group and for 62 days (range 31–76 days) in the placebo group. Thus, information on allergic symptoms was available from approximately 90% of all pollen days.

Efficacy

Symptom load was measured using a scale with a range between 0 (no symptoms) and 3 (severe symptoms). The mean symptom load of the subjects varied between 0.5 and 1.0 during the whole pollen season. A reduction by 39% of the median symptom load score in favour of omalizumab was observed (Fig. 2). The net mean difference between both treatments was -0.21 score points (adjusted for centre) which was statistically significant with the non-parametric Wilcoxon test ($P = 0.0464$). Differences between the two treatment groups were more pronounced in the analyses with the PP population (mean difference: -0.25 ; $P = 0.0116$, Wilcoxon test). The ANOVA model with logarithmically transformed data showed significant differences between the two treatments in both analysis populations (ITT: $P = 0.03218$, 95% point estimate: -0.14 , confidence interval: $[-0.27, -0.01]$, PP: $P = 0.01345$, 95% point estimate: -0.16 , confidence interval: $[-0.29, -0.03]$). When analysing the two components of the symptom load score, it is obvious that the symptom severity scale is the main contributor to the observed difference in the primary efficacy measure, while groups did not differ in use of rescue medication (Table 2).

Compared with the placebo group, omalizumab treatment also reduced impairment to daily life activities of both, with respect to general asthma symptoms (ACQ) and to specific quality of life changes due to asthma (AQLQ) and, in tendency, due to rhinoconjunctivitis (RQLQ) (Table 2).

GETE assessment by investigators and patients, using a five-point scale, was in favour of omalizumab: 'excellent' and 'good' treatment effectiveness (pooled categories) was reported by the investigators in 72.7% for omalizumab and in 36.9% for placebo, by the patients in 77.3% and 46.2%, respectively. 'Poor' treatment effectiveness was seen in 6.1% and 13.8% by the investigators, and in 1.5% and in 13.8% by the patients, respectively ($P = 0.0001$ for all analyses, using the Mantel-Haenszel χ^2 -test or Fisher's exact test) (Fig. 3).

Lung function as assessed with mean FEV₁% predicted was slightly better in the omalizumab group (93.5%) than in the placebo group (90.9%, $P = 0.0694$, ANCOVA adjusted for centre and baseline measure), but there were no differences in the mean PEF measure (451 L/min vs. 442 L/min, $P = 0.2954$).

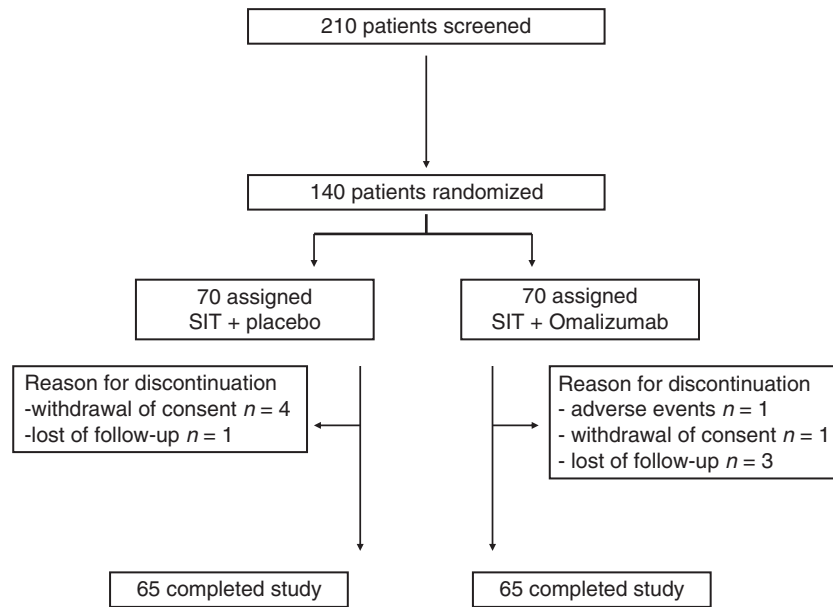


Fig. 1. Flowchart showing progress of participants through the trial.

Table 1. Demographic data, baseline characteristics, treatment of patients and pollen days (all treated patients)

	Depigoid + omalizumab	Depigoid + placebo
<i>n</i> (female/male)	70 (31/39)	70 (30/40)
Age (years), median (range)	30 (11–46)	33 (12–45)
Age groups, <i>n</i> (%)		
11–18	16 (22.9)	16 (22.9)
19–29	19 (27.1)	12 (17.1)
30–46	35 (50.0)	42 (60.0)
Smoker, <i>n</i> (%)	9 (12.9)	8 (11.4)
BMI (kg/m ²), median (range)	24.7 (16.6–36.3)	23.1 (16.0–40.0)
Total IgE (kU/L), median (range)	145 (20.1–641.3)	133.5 (31.6–548.9)
Grass pollen sIgE, median (range)	29.7 (0.7–100)	21.2 (0.7–100)
Rye pollen sIgE, median (range)	30.8 (0.7–100)	21.5 (0.7–100)
Allergies, <i>n</i> (%)		
Seasonal (pollen)	22 (31.4)	28 (40.0)
Food	2 (2.9)	6 (8.6)
Animal	0	1 (1.4)
FEV ₁ % predicted, median (range)	98 (76–120)	98 (70–132)
Omalizumab/placebo application, <i>n</i> (%)		
2 weekly	29 (41.4)	23 (32.9)
4 weekly	41 (58.6)	47 (67.1)
Drug exposure (days), median (range)		
Depigoid	113.0 (29–136)	113.0 (1–226)
Omalizumab/placebo	113.0 (1–135)	113.0 (1–141)
Drug dosages (cumulative in mg), median (range)		
Depigoid	2.5 (1.0–2.6)	2.5 (0.5–3.1)
Omalizumab/placebo*	1500.0 (225–3375)	1500.0 (150–3375)
Pollen exposure [†] (days), median (range)	68 (41–87)	

BMI, body mass index; FEV₁, forced expiratory volume in 1 s.

*There were 3 patients with no rush-IT but conventional Depigoid titiation.

[†]For definition of pollen days, see text in method section.

Tolerability and safety

Approximately half of the patients in each treatment group were affected by at least one adverse event (AE; Table 3). The most frequently reported System Organ Class was 'application site conditions' and 'infections and infestations'. More patients in the depigmented SIT plus placebo group experienced such drug-related AEs than in the depigmented SIT plus omalizumab group. This difference is mainly due to local reactions (Table 3). More patients in the depigmented SIT plus placebo than in the depigmented SIT plus omalizumab group reported itching (17.7% vs. 10.3%), pain (8.9% vs. 2.9%) or any other reaction (22.1% vs. 11.8%) when asked specifically for local reactions towards the application of study medication. However, these differences were not statistically significant. We observed no systemic reactions to the study drug. No clinically relevant abnormalities were identified in the analysis of laboratory variables and vital signs.

Discussion

This study investigated the combined effect of the monoclonal anti-IgE antibody omalizumab and SIT in the management of patients with allergic rhinoconjunctivitis

and co-morbid seasonal asthma incompletely controlled by conventional pharmacotherapy. We were able to show a reduction of 39% in symptom load – a score which combines symptom severity and rescue medication use – during the entire pollen season for omalizumab+SIT-treated patients as compared with those on SIT alone. This observation strongly supports the primary hypothesis of the study and suggests that combination therapy provides a statistically significant and clinically relevant improvement on current standard therapy for the management of patients with SAR and co-morbid seasonal asthma.

The new concept, which targets IgE with a humanized monoclonal antibody, is proven in numerous clinical trials comprising patients with either allergic rhinoconjunctivitis [11, 17, 20] or allergic asthma [18, 19, 27]. These findings support the critical role of IgE in basic regulatory mechanisms of allergic inflammation. It is of particular interest that the basic mechanisms of SIT show an overlap with the effects of omalizumab [12–16]. Recently, it has been shown that SIT with ragweed alone induced serum regulatory antibodies that partially blocked binding of allergen–IgE complexes to B cells. Treatment with anti-IgE, which blocked IgE binding to CD23 directly, completely inhibited allergen–IgE binding. The combination of SIT and anti-IgE resulted in prolonged inhibition of allergen–IgE binding compared with either treatment alone, which might contribute to enhanced clinical efficacy [28].

Until now, two clinical trials have been conducted which have consistently shown an increase in the clinical efficacy of a combined therapy of SIT+omalizumab in patients with allergic rhinoconjunctivitis for the first year [11, 17]. We have reported the first study, which extended the previous findings on a population of individuals with SAR and co-morbid seasonal asthma. In line with published data, we were able to confirm the effect of a combined therapy with omalizumab on symptom load, asthma control and asthma or rhinoconjunctivitis quality of life scores during the pollen season. The difference in our primary endpoint, symptom load between both

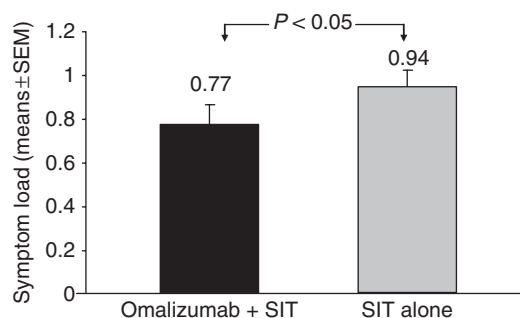


Fig. 2. Symptom load during the pollen season. *P*-values associated with the Wilcoxon-test. SIT, specific immunotherapy.

Table 2. Analysis of secondary efficacy variables (intention-to-treat population)

Efficacy variable	Adjusted* mean		Adjusted† treatment difference	95% confidence interval	<i>P</i> -value†	<i>P</i> -value*
	Omalizumab	Placebo				
Symptom severity	0.38	0.59	–0.21	[–0.35, –0.07]	0.0044	0.0157
Rescue medication	0.38	0.38	0	[–0.17, 0.17]	0.9807	0.2956
ACQ	1.63	1.96	–0.33	[–0.63, –0.03]	0.0295	0.0497
AQLQ	6.41	6.07	0.34	[0.04, 0.65]	0.0293	0.1093
RQLQ	1.80	2.11	–0.32	[–0.64, –0.01]	0.0537	0.0801

*Wilcoxon test: symptom, two-sided *P*-values.

†ANOVA model with treatment and centre as fixed effects.

Assessments from the individual last visit in the study (last observation carried forward).

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

groups, was triggered mainly by symptom severity. In contrast, the second component of the symptom load, rescue medication use, was comparable in both groups. However, symptom severity and the use of rescue medications are strictly interdependent. While some individuals prefer to take only a few rescue medications and tolerate

more symptoms, others behave in a quite opposite way. Therefore, the World Allergy Association (WAO) recently recommended using a combined symptom and medication score as primary endpoint, indicating that each of these account for half of the clinical burden of the disease [29]. The majority of the analyses of secondary efficacy variables showed more favourable results for omalizumab plus SIT than for SIT alone. Besides having an effect on the severity of symptoms, pronounced effects could be found in the quality of life scores (asthma control, asthma or rhinoconjunctivitis quality of life scores) and most convincingly on GETE by investigators and patients. Effectiveness was assessed as 'excellent' or 'good' in three out of four patients in the omalizumab plus depigmented SIT group, compared with only one-third of the SIT group, which clearly shows a better treatment outcome in the combination group. In line with previously published data, our results indicate that lung function parameters are not sensitive enough to mirror treatment effectiveness of omalizumab in patients with mild to moderate asthma [18]. In contrast, patients with moderate to severe asthma with limited lung function parameters at baseline showed significant improvement in PEF and FEV₁% predicted after omalizumab treatment compared with placebo [27].

The therapeutic benefit of SIT is widely accepted and its efficacy in allergic rhinoconjunctivitis is undoubted [6]. Unfortunately, in patients with severe asthma, SIT is limited due to safety concerns because of the potential risk of severe asthma exacerbation [9, 10]. However, complete asthma control often does not occur with pharmacotherapy. Against this background, great efforts have been made to simultaneously augment efficacy of SIT and the safety. This can be achieved by developing

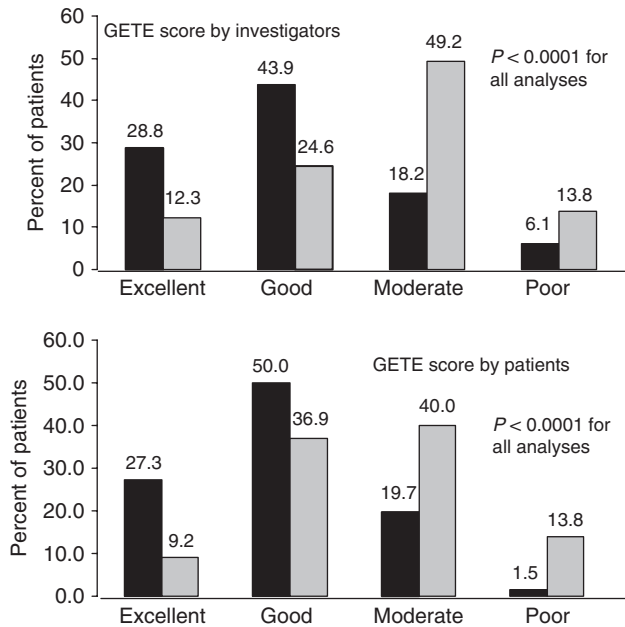


Fig. 3. Global evaluation of treatment effectiveness (GETE) on asthma control by investigator (above) and patients (below). Black bars: Omalizumab plus specific immunotherapy (SIT), grey bars: SIT alone. Two patients of the omalizumab plus SIT group without GETE ratings. *P*-values associated with the Mantel-Haenszel χ^2 -test.

Table 3. Adverse events in most frequently affected body systems ($\geq 5\%$ in any group, safety population)

	Number of patients (%)	
	Depigoid + omalizumab	Depigoid + placebo
Patients studied, <i>n</i> (%)		
Total no. of patients with treatment	70	70
Total no. of patients with adverse events	36 (51.4)	38 (54.3)
Adverse events, <i>n</i> (%)		
General disorders and administration site conditions		
Local reaction	7 (10.0)	12 (17.1)
Application site reaction	2 (2.9)	4 (5.7)
Injection site pruritus	2 (2.9)	3 (4.3)
Injection site swelling	–	3 (4.3)
Infections and infestations		
Nasopharyngitis	8 (11.4)	9 (12.9)
Sinusitis	2 (2.9)	3 (4.3)
Respiratory, thoracic and mediastinal disorders		
Cough	–	5 (7.1)
Nervous system disorders		
Headache	4 (5.7)	7 (10.0)

strategies to dispense allergenic material that will retain immunogenicity and desensitize patients but at the same time will not cause allergic reactions. New approaches to SIT may include alternate routes, adjuvant peptides, fusion proteins and recombinant allergens [30]. So far, one promising approach has been the combination of omalizumab with SIT. In this context, favourable health effects and an increased safety profile of a combined therapy with omalizumab plus SIT in patients with mild asthma have to be evaluated. Potentially, these results disclose new perspectives for the application of SIT in patients with moderate to severe asthma. Very recently, Casale *et al.* [17] impressively demonstrated that omalizumab pre-treatment enhances the safety of rush-SIT for ragweed-allergic rhinoconjunctivitis. Significantly more patients in the SIT-only group vs. the group receiving omalizumab plus SIT experienced serious adverse events. These data demonstrate the benefit of omalizumab pre-treatment in allergen-specific immunotherapy in providing substantial protection against acute allergic reactions, including anaphylaxis.

In contrast to the study published by Casale, we used Depigoid as depigmented SIT treatment, which offers a possible safety advantage over aqueous allergen extracts [21]. The most frequently reported AEs, such as local reactions, tend to occur less frequently in the omalizumab plus SIT group than in the SIT group; however, the differences were not statistically significant. All local reactions in the omalizumab plus SIT group were classified as 'mild', and even during the rush-SIT period, no systemic reaction occurred.

One limitation of our study is that the characterization of our study population is based on a retrospective evaluation of allergic complaints during the last pollen season. A more detailed acquisition of asthma severity by recording clinical symptoms, rescue medication and lung function measurement during a baseline season would have strengthened our results. Although we did not compare the results in the different treatment arms with a pure placebo group, we were able to answer our original research question, which was to demonstrate the superiority of the combined treatment over SIT alone. Anyway, the superiority of these both treatment options over placebo has already been shown in previous reports [17–20, 31–33]. There are now several open-label studies which have shown that SIT also lowers the onset of new sensitization and the progression from allergic rhinoconjunctivitis to bronchial asthma [34, 35]. Until now, there have been no comparable data describing the long-term effects of a combined therapy of omalizumab and SIT. Therefore, we will follow up our population for 2 years to explore the clinical symptoms and possible onset of new sensitization in both groups.

Taken together, SIT as a curative therapeutic option for allergic rhinoconjunctivitis and asthma is a unique inter-

vention that should be applied at an early stage of the disease. Here, we have shown that a combined therapy of omalizumab and SIT has an excellent safety profile. Moreover, omalizumab+SIT reduce symptom load in a way that is statistically significant and clinically relevant, as compared with SIT alone. The clinical implication of our findings is that patients with moderate to severe allergic asthma pre-treated with omalizumab might also benefit in the future from SIT as a causal treatment option.

Acknowledgements

The authors thank all participating investigators of the DUAL (Depigoid und OmalizUmab bei Asthma SaisonaL) study: M.V. Kopp, U. Lütke 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. Rothoefelt (Bochum), W. Kamin, G. Sahin and B. Klär-Hlawatsch (Mainz), R. Brehler and P. Hemfort (Münster), 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. Zingler 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 study was supported by a grant from Novartis Pharma GmbH, Nuernberg.

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