

Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis

Joachim Kuehr, MD,^a Jens Brauburger, PhD,^b Stefan Zielen, MD,^c
Uwe Schauer, MD,^d Wolfgang Kamin, MD,^e Andrea Von Berg, MD,^f
Wolfgang Leupold, MD,^g Karl-Christian Bergmann, MD,^h Claudia
Rolinck-Werninghaus, MD,ⁱ Michael Gräve, MSc,^b Thomas Hultsch, MD,^j Ulrich
Wahn, MD,ⁱ and the Omalizumab Rhinitis Study Group Freiburg, Nuernberg, Bonn,
Bochum, Mainz, Wesel, Dresden, Bad Lippspringe, and Berlin, Germany, and Basel, Switzerland

Background: Specific immunotherapy (SIT) and treatment with monoclonal anti-IgE antibody have complementary modes of action.

Objective: The purpose of this study was to determine whether combined therapy could provide better efficacy than either treatment alone.

Methods: We conducted a randomized, double-blinded trial to assess the efficacy and safety of subcutaneously administered anti-IgE (omalizumab) or placebo in children and adolescents with seasonal allergic rhinitis in both a birch pollen season and a grass pollen season (sequential seasons together lasting an average of 84 days). There were 4 treatment arms. Each subject was started on SIT-birch or SIT-grass, and anti-IgE or placebo was started before and maintained during the anticipated pollen seasons (a total of 24 weeks). The primary efficacy variable was symptom load, the sum of daily symptom severity score plus rescue medication use.

Results: A total of 221 subjects (intent-to-treat population) aged 6 to 17 years were analyzed for efficacy. Combination therapy reduced symptom load over the 2 pollen seasons by 48% ($P < .001$) over SIT alone. When analyzed separately by season, the 2 groups receiving unrelated SIT were considered placebo controls. In the grass season, symptom loads were as follows: unrelated (birch) SIT + placebo, 0.89 (reference value); unrelated (birch) SIT + anti-IgE, 0.49 (–45%); SIT-grass + placebo, 0.61 (–32%); SIT-grass + anti-IgE, 0.26 (–71%).

Conclusion: Anti-IgE therapy conferred a protective effect independent of the type of allergen. Additional clinical benefit was demonstrated in both pollen seasons, whether there was

coverage by SIT or not. This combination might prove useful for the treatment of allergic rhinitis, particularly for polysensitized patients. (*J Allergy Clin Immunol* 2002;109:274-80.)

Key words: Anti-IgE, omalizumab, specific immunotherapy, seasonal allergic rhinitis, children, adolescents

The management of allergic diseases is based on the general principles of environmental control (allergen avoidance), pharmacologic therapy, allergen immunotherapy, and patient education.^{1,2} Specific immunotherapy (SIT) can be an effective treatment for allergic rhinitis and allergic asthma³ if adequate doses of standardized allergens are administered,⁴ with the possibility of long-term benefits extending beyond the course of treatment.⁵ However, there are safety concerns associated with SIT, particularly the risk of systemic anaphylactic reactions (in <1% of patients receiving conventional immunotherapy, increasing to >36% in patients receiving rush protocols⁶). The clinical effect of SIT might be incomplete in the first year of therapy,⁷ especially in polysensitized patients.⁸

The monoclonal anti-IgE antibody, omalizumab, lowers levels of serum free IgE in human beings and reduces IgE-mediated symptoms,⁹ regardless of the allergen specificity (and biological role) of the IgE involved. Efficacy of anti-IgE versus placebo in reducing the severity of symptoms of seasonal allergic rhinitis (SAR) and in improving rhinoconjunctivitis-specific quality of life has been reported.⁹ Efficacy in patients with allergic asthma has also been reported, anti-IgE being used as an intravenously administered formulation¹⁰ and, more recently, as a subcutaneous injection given every 2 or 4 weeks.¹¹ In these studies, anti-IgE treatment significantly reduced the requirement for concomitant medication (antihistamines for rhinitis, inhaled corticosteroids for asthma).

We were interested in determining whether the combination of “passive immunization” (with anti-IgE) and active immunization (SIT, with standardized allergen extracts) would prove clinically superior to SIT alone. The objective of our study was to investigate the effect of anti-IgE in combination with SIT in polysensitized children and adolescents with moderate-to-severe SAR who had not been adequately controlled by pharmacotherapy during the previous season.

From ^aUniversity Children's Hospital, Freiburg; ^bNovartis Pharma GmbH, Nuernberg; ^cChildren's Hospital Medical Center, Bonn University; ^dUniversity Children's Hospital, Bochum; ^eChildren's Hospital, Mainz University; ^fMarien-Hospital, Wesel; ^gUniversity Children's Hospital, Dresden; ^hAuguste-Viktoria Klinik, Bad Lippspringe; ⁱthe Department of Pediatric Pneumology and Immunology, Charité Humboldt University, Berlin; and ^jNovartis Pharma AG, Basel.

Supported by Novartis Pharma GmbH, Nuernberg, Germany, and Novartis Pharma AG, Basel, Switzerland.

Received for publication November 1, 2001; revised November 28, 2001; accepted for publication November 29, 2001.

Reprint requests: Ulrich Wahn, MD, Department of Pediatric Pneumology and Immunology, Charité Humboldt University, Augustenburger Platz 1, D-13353 Berlin, Germany.

Copyright © 2002 by Mosby, Inc.

0091-6749/2002 \$35.00 + 0 1/81/121949

doi:10.1067/mai.2002.121949

Abbreviations used

ITT: Intention-to-treat
SAR: Seasonal allergic rhinitis
SIT: Specific immunotherapy

METHODS

Study design

This was a randomized, double-blinded, placebo-controlled, parallel-group study conducted in 17 centers in Germany. We enrolled children and adolescents aged 6 to 17 years, each with a clinical history of birch pollen-induced and grass pollen-induced SAR within at least the previous 2 years. The presence of IgE specific for birch and grass pollen was confirmed in all subjects (≥ 0.7 U/L; CAP class, ≥ 2). Subjects with perennial allergic rhinitis were excluded, as were (a) those with total serum IgE levels outside the range 30 to 1300 IU/mL and (b) those who had body weight >100 kg for reasons of dosing. Signed informed consent was obtained from all subjects and/or their guardians, and the study design was approved by the ethics committees of the participating centers.

The pollen seasons for birch and grass in Germany are sequential and well defined; they run from February to July, depending on the location of the center. Pollen counts were assessed systematically in all centers, and the start and the end of the pollen season were each defined as a threshold of >10 grains/m³/24 hours for 3 consecutive days for birch and >5 grains/m³/24 hours for grass. The efficacy analysis was based on diary information collected only during the defined pollen seasons (on average, a total of 84 days in this study).

Each subject was randomized to one of 4 treatment groups. For at least 14 weeks before the start of the birch pollen season, 2 of the groups (A and B) received SIT-birch given subcutaneously (ALK-Scherax/Abello, Berlin, Germany); the other 2 groups (C and D) received SIT-grass. The birch pollen extract contained 12.3 μ g of major allergen (bet v 1) per 100,000 SQ units. The grass pollen extract, a mix of 6 grasses and secale, contained the following quantities of major allergen (in μ g per 100,000 SQ units): *Phleum pratense*, 20.2; *Avena eliator*, 12.0; *Dactylis glomerata*, 12.0; *Lolium perenne*, 12.5; *Poa pratense*, 15.2; *Festuca pratense*, 18.6; *Secale cereale*, 10.2. The grass pollen extract thus provided an average of 14.4 μ g of major allergen per 100,000 SQ units. For both birch pollen and grass pollen, 12 SIT injections at 1-week intervals were given during the build-up phase before the birch season; this was followed by 5 maintenance injections at 4-week intervals. In 27 subjects (12.2%), build-up continued beyond the 12th week. A total of 181 patients (81.9%) reached the maintenance dose of 100,000 SQ units, and a mean maintenance dose of 86,905 SQ units was achieved. The mean cumulative dose of SIT-birch allergen extracts administered before the birch season was 394,300 SQ units; the mean cumulative dose of SIT-grass allergen extracts administered before the grass season was 478,000 SQ units. After 12 weeks of SIT titration, placebo (groups A and C) or anti-IgE (omalizumab; groups B and D) was added for 24 weeks (Fig 1).

Anti-IgE or placebo was given in parallel to the SIT maintenance injections, the result being no additional office visits for patients receiving the study drug at 4-week intervals. Additional visits were required only if anti-IgE/placebo was administered at 2-week intervals (in patients with high IgE levels or high body weight). Anti-IgE was administered subcutaneously on the basis of body weight and serum total IgE, providing a dose of at least 0.016 mg/kg per IU/mL of IgE every 4 weeks.

Daily symptom severity scores (eyes and nose) and rescue medication usage were assessed during the pollen seasons. The symptom severity score was the mean of the daily symptom severity scores during the pollen seasons; the rescue medication score was the mean

of the daily rescue medication scores during the pollen seasons. The primary efficacy variable was the daily symptom load—ie, the sum of the mean daily symptom severity score plus the mean daily rescue medication score. For the symptom severity score, the severity of each of the following 7 symptoms was recorded daily by patients on a 4-point scale (0 = none; 3 = severe): itchy, runny, or stuffy nose or sneezing; itchy, watery, or red eyes. Rescue medication usage was scored daily on a 4-point scale (0 = no rhinitis medication; 1 = topical nasal, ocular, or lung treatment apart from corticosteroids; 2 = systemic antihistamines; 3 = systemic or topical corticosteroids for nose or lung). When more than one rescue medication was used on the same day, only the maximal score medication was recorded. Patients were supplied with certain permitted rescue medications for use as needed according to a predefined schedule: topical levocabastine (eye drops and nasal spray) and inhaled salbutamol (step 1), cetirizine (step 2), and prednisolone (step 3). Leukotriene antagonists and cromones were not permitted.

All adverse events were recorded and monitored. Hematology evaluations, blood chemistry evaluations, urinalysis, baseline IgE determination, and specific IgE assays were carried out at a central laboratory. Hematology evaluations included hemoglobin, hematocrit, white blood cell count and differential, red blood cell, and platelet counts. Blood chemistry included sodium, potassium, protein, albumin, calcium, total bilirubin, serum glutamic pyruvate transaminase, serum glutamic oxaloacetate transaminase, alkaline phosphatase, glucose, creatinine, blood urea nitrogen, and uric acid.

Statistical analysis

The Wilcoxon rank sum test was used for confirmatory analysis of efficacy variables. Mean ranks were used for tied observations, the test being based on normal approximations. The predefined multiple type I error was set to 5%. Corresponding 2-sided CIs were calculated.

All analyses were performed on the intention-to-treat (ITT) population. The ITT population was defined as all patients in the safety population for whom an efficacy evaluation was performed (the safety population comprised all patients who received at least 1 dose of anti-IgE or placebo).

RESULTS

Patients

In all, 225 patients were randomized and 219 completed the study. A total of 221 patients (the ITT population) received combination therapy and were analyzed for efficacy (Table I). The safety population included an additional patient who started treatment but withdrew consent before the birch pollen season.

Efficacy

The symptom load during the entire pollen season (birch and grass) is shown in Fig 2, A. A reduction of 48% in the median symptom load score in favor of anti-IgE versus placebo was observed for both analyses, SIT-birch + placebo vs SIT-birch + anti-IgE ($P < .001$) and for SIT-grass + placebo vs SIT-grass + anti-IgE ($P < .001$).

For the birch season (Fig 2, B), the SIT-grass therapy (group C, the unrelated grass allergen for that season) was considered a placebo control (reference) for SIT-birch. In comparison with the reference (group C), anti-IgE (group D) reduced symptom load by 39% ($P = .1$). Unexpectedly, the relevant SIT-birch (group A) showed no improvement over group C (symptom load increase, 5%; $P = .43$).

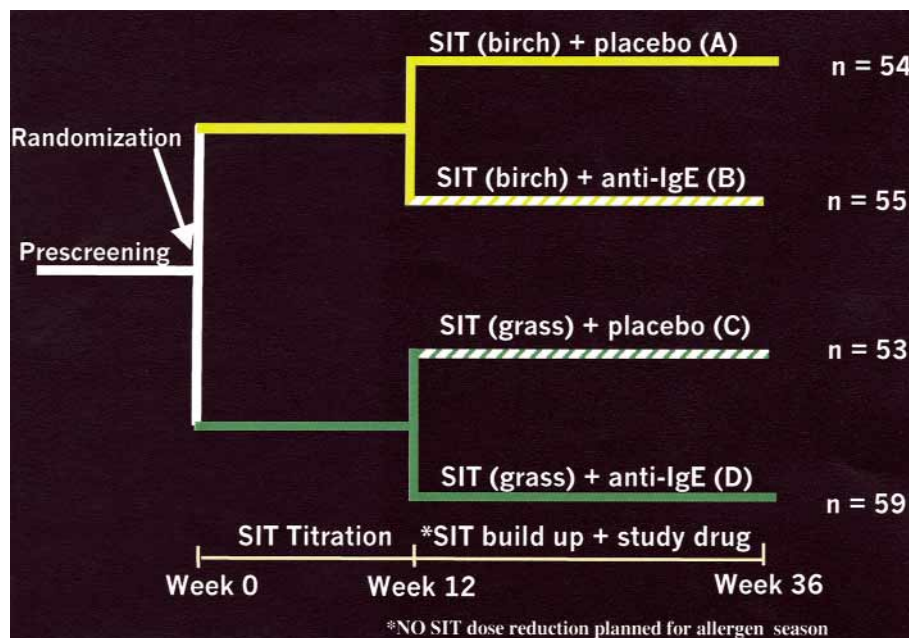


FIG 1. Study design.

TABLE I. Baseline characteristics of the subjects (ITT population)

Characteristic	Group				All subjects
	A: SIT-birch + placebo	B: SIT-birch + anti-IgE	C: SIT-grass + placebo	D: SIT-grass + anti-IgE	
n (F/M)	54 (23/31)	55 (24/31)	53 (15/38)	59 (31/28)	221 (93/128)
Age (y)*	12 (6-17)	12 (6-17)	12 (6-17)	12 (6-17)	12 (6-17)
Duration of SAR (y)†	5 (3, 13)	6 (3, 13)	5 (3, 13)	6 (3, 12)	5 (3, 12)
Total IgE (kU/L)‡	302 (52, 880)	315 (71, 913)	409 (53, 745)	413 (87, 962)	345 (75, 906)
Specific IgE‡ to birch (kU/L)‡	9 (1, 125)	6 (1, 73)	5 (0, 125)§	10 (1, 125)	7 (1, 125)
Specific IgE‡ to grass (kU/L)‡	52 (2, 125)	66 (2, 125)	58 (1, 125)	75 (3, 125)	62 (2, 125)

SIT, Specific immunotherapy; SAR, seasonal allergic rhinitis; F, female; M, male.

*Data are presented as median (range) values.

†Data are presented as median values; (5%, 95%) percentiles are given in parentheses.

‡Specific IgE values greater than 100 were set to 125; values less than 0.35 were set to 0.

§One patient with the 0 value at baseline had positive IgE to grass within 3 months before baseline and a clear clinical history of grass-induced symptoms.

The combination of relevant SIT with anti-IgE (group B), however, showed the lowest symptom load score (48% reduction from group C, $P = .08$). Moreover, in comparison with relevant SIT alone, the addition of anti-IgE reduced symptom load by 50% (A vs B, $P = .003$).

For the grass pollen season (Fig 2, C), SIT-birch alone (group A) was considered a placebo control (reference). Addition of anti-IgE (group B) reduced symptom load by 45% in comparison with group A ($P < .001$). The relevant SIT-grass (group C) showed the expected outcome, reducing symptom load by 32% in comparison with reference group A ($P = .1$). The combination of relevant SIT and anti-IgE (group D) had the maximum effect, with a 71% decrease from group A ($P < .001$). Finally, anti-IgE also had a significant effect over and above the relevant SIT (group D vs group C), decreasing symptom load by 57% ($P = .001$). Fig 2, C also illustrates that SIT had an additive effect to anti-IgE, inasmuch as the group receiving anti-IgE plus relevant SIT (group D) had a significantly

lower symptom load ($P = .032$; data not shown) than those receiving anti-IgE plus the unrelated SIT (group B).

When symptom load was broken down into its 2 components, rescue medication score and symptom severity, it was apparent that rescue medication reduction was a major contributing factor to improved symptom load. In the SIT-birch group, the median rescue medication score was reduced by 78% (0.27 vs 0.06; $P < .001$). In the SIT-grass group, the median rescue medication score decreased by 81% (0.16 vs 0.03; $P = .001$). The use of corticosteroids was recorded by 15 patients in the pooled SIT + placebo group (including 11 in the SIT-birch group during the grass pollen season) and 5 patients in the SIT + anti-IgE group. The proportion of days when rescue medication was used was significantly lower in the SIT + anti-IgE groups than in the placebo groups (median percent of days of the entire pollen season, 4.36 vs 15.07; $P < .001$). The proportion of days when allergy symptoms occurred was also significantly lower in the SIT + anti-

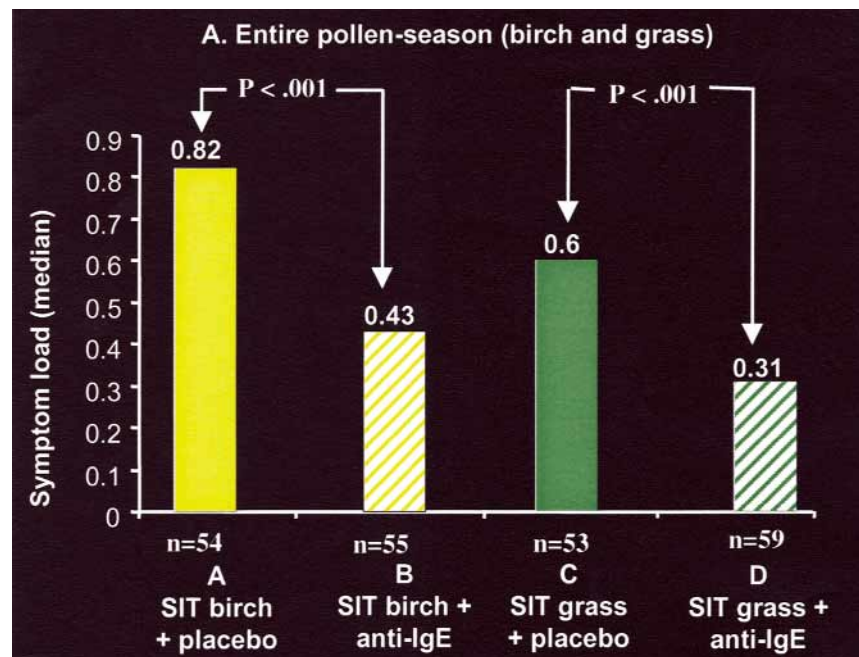


FIG 2. A, Symptom load during the entire pollen season (birch and grass).

IgE groups versus placebo (median percent of days of the entire pollen season, 58.6 vs 79.3; $P < .001$).

The second component of symptom load, symptom severity, decreased significantly with the addition of anti-IgE in the separate SIT groups and overall (median scores from pooled data, 0.40 vs 0.24; $P < .001$).

Safety

A total of 221 patients entered the pollen season and received combination therapy; 219 patients completed the study. For the safety analysis, all anti-IgE patients were pooled ($n = 114$) and compared with the rest of the population. There were no serious adverse events related to study drug administration reported in the study. Eighty percent of the patients in the 2 treatment groups reported adverse events (Table II), of which the most frequently reported in both groups were cough, headache (each in approximately 25% of patients), and upper respiratory tract infection (approximately 15%). Interestingly, eczema lesions were reported exclusively in the placebo group; there were none in the anti-IgE group. Events considered related to the study drug (either SIT or anti-IgE/placebo) were more frequent in the SIT + anti-IgE groups (25%) than in the SIT + placebo groups (16%). This difference was already observed during the titration period (SIT injections only) and hence seems unrelated to anti-IgE.

Injection site reactions, defined as redness, swelling, induration, pain, reduced mobility, or any combination of these, were assessed for SIT and anti-IgE/placebo injection sites separately. Such reactions were common and did not differ significantly between the 2 types of treatment (in 77% to 92% of patients at the anti-IgE/placebo site and in 78% to 91% of patients at the SIT site).

Urticaria occurred in 2 patients on anti-IgE and in no

patients on placebo during the 24-week combination treatment period. Both cases were moderate, were considered unrelated to the study drug, and resolved within 1 week. There were no cases of anaphylaxis. The frequency of adverse events in the younger children (6-12 years old; $n = 132$) did not differ from that in the overall population ($n = 222$).

Of the 900 blood samples taken during this study, isolated occurrences of platelet counts $<150 \times 10^9/L$ were seen during the treatment phase on 13 occasions (10 subjects, 9 on active and 1 on placebo treatment; range, 47 to $148 \times 10^9/L$). In addition, platelet counts in 4 subjects were low before anti-IgE administration. Both in subjects with low values during treatment and in subjects with low baseline values, the levels returned to normal counts ($>150 \times 10^9/L$) at the subsequent blood sampling while the subjects were receiving anti-IgE treatment. No bleeding was observed.

DISCUSSION

Complex cases of SAR—eg, patients with multiple allergic symptoms incompletely controlled by conventional pharmacotherapy or immunotherapy—represent a clinical challenge. In this study we investigated the benefit of anti-IgE in the management of these patients.

The burden of the disease was assessed with a symptom load score, a construct combining symptom severity and rescue medication use. We propose this score to be more robust than either symptom severity score or rescue medication score alone, inasmuch as it assesses the benefit for patients regardless of their preference to reduce medication or to reduce clinical symptoms.

The results show a reduction of 48% in symptom load for the entire combined pollen season (average length, 84 days)

Asthma, rhinitis,
other respiratory
diseases

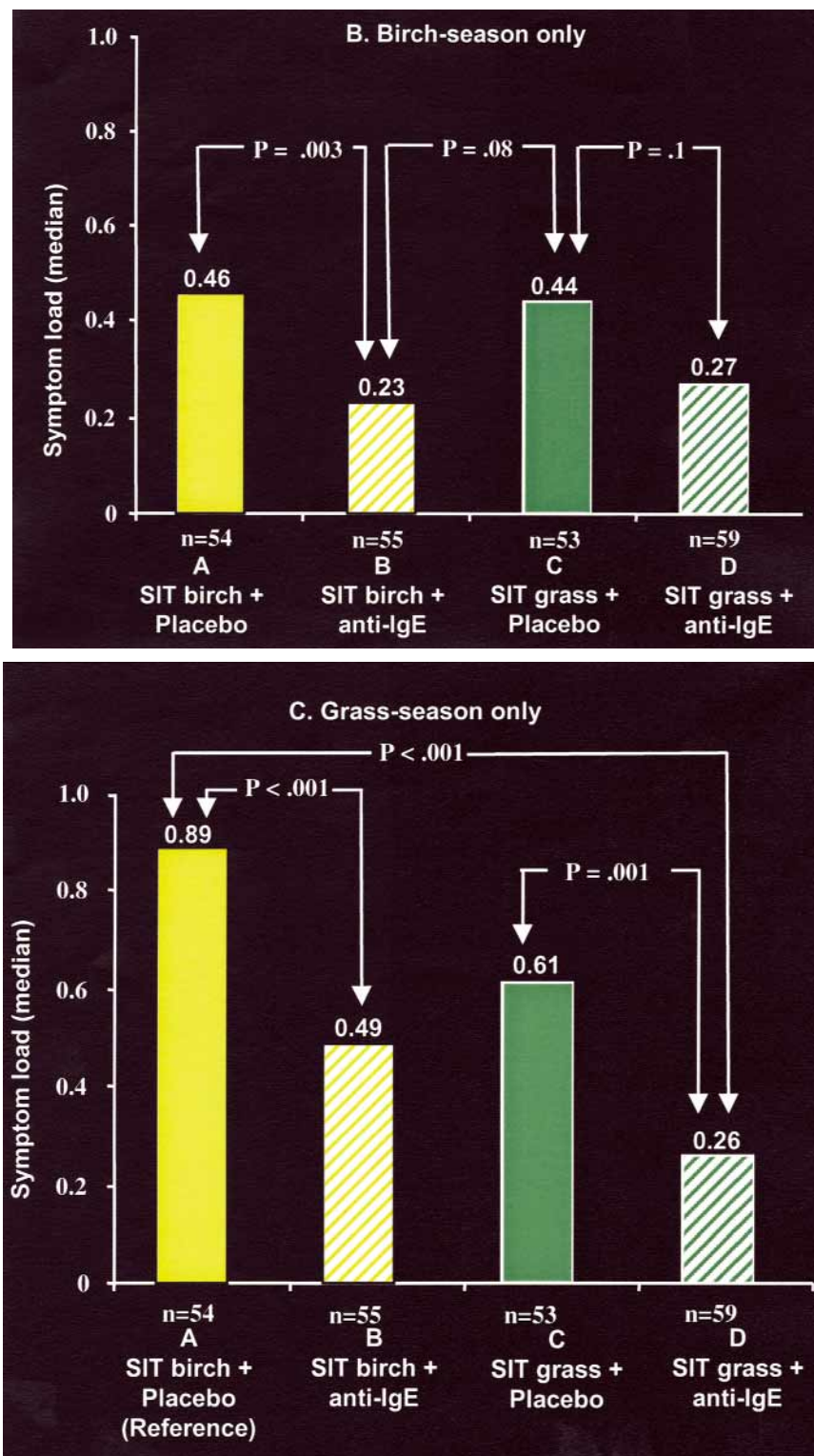


FIG 2. (continued) **B**, Symptom load during the birch pollen season. **C**, Symptom load during the grass pollen season.

for SIT + anti-IgE-treated patients in comparison with those on SIT alone. This observation strongly supports the primary hypothesis of the study and suggests that combination therapy is a meaningful improvement over current standard

therapy for the management of complex cases of SAR. Moreover, when analyzed by season, anti-IgE reliably reduced allergen-induced symptom load regardless of the nature of the allergen and the efficacy of conventional SIT.

TABLE II. Adverse events in most frequently affected body systems ($\geq 5.0\%$ in any group, safety population)

System organ class and adverse event	No. of patients (%)	
	SIT pooled + anti-IgE (n = 114)	SIT pooled + placebo (n = 108)
Ear and labyrinth		
Earache	6 (5.3)	3 (2.8)
Gastrointestinal		
Sore throat*	16 (14.0)	7 (6.5)
Nausea	8 (7.0)	8 (7.4)
Diarrhea*	7 (6.1)	6 (5.6)
General disorders and administration site conditions		
Injection site pain	7 (6.1)	2 (1.9)
Injection site reaction*	7 (6.1)	1 (0.9)
Pyrexia	6 (5.3)	5 (4.6)
Injection site edema	6 (5.3)	4 (3.7)
Peripheral swelling	6 (5.3)	4 (3.7)
Injection site pruritus	5 (4.4)	6 (5.6)
Infections and infestations		
Upper respiratory tract infection*	17 (14.9)	13 (12.0)
Nasopharyngitis	16 (14.0)	14 (13.0)
Influenza	1 (0.9)	7 (6.5)
Nervous system		
Headache*	29 (25.4)	25 (23.2)
Respiratory, thoracic, and mediastinal		
Cough	30 (26.3)	25 (23.2)
Dyspnea*	6 (5.3)	5 (4.6)
Rhinitis*	2 (1.8)	9 (8.3)
Asthma*	2 (1.8)	7 (6.5)
Skin and subcutaneous tissue disorders		
Eczema*	0 (0)	7 (6.5)
Pruritus*	6 (5.3)	6 (5.6)

*Not otherwise specified.

In the first pollen season (birch; average length, 23 days) anti-IgE reduced symptom load in combination with either form of SIT: related SIT (group B vs group C, 48%) or placebo SIT (group C vs group D, 39%). The unexpected lack of efficacy of SIT-birch (group A vs group C) was possibly caused by early pollen exposure—before adequate cumulative SIT doses were administered—and limits our findings during the first pollen season (birch). The observed poor effect of SIT-birch might also reflect the very modest symptom load score in this group.

In the second pollen season (grass; average length, 61 days), marked benefits were observed with the addition of anti-IgE: a 71% reduction of symptom load in combination with related SIT-grass (group A vs group D) and a 45% improvement over unrelated SIT (group A vs group B). The expected effect of SIT-grass was seen in the grass season (group A vs group C), likely related to the higher cumulative dose of allergen extract administered before grass pollen exposure. It is also of interest to examine whether SIT adds to the response to anti-IgE, given that it has already been established that anti-IgE is an effective treatment for seasonal allergic rhinitis.⁹ The significant 47% decrease in symptom load for the patients receiving the relevant (grass) SIT with anti-IgE in comparison with those receiving anti-IgE with the unrelated (birch) SIT indicates that there is an additive effect of the 2 forms of treatment.

The changes in rescue medication and symptom severity scores mirrored the overall symptom load, though to differing extents: anti-IgE reduced symptom scores by 35% to 45% and rescue medication scores by 78% to

81%. Patients receiving anti-IgE required almost no additional rhinitis medication, which is of particular interest in a pediatric population.

The mean exposure to anti-IgE before the start of the birch pollen season was 45 days. This contrasts with the findings in the study by Ädelroth et al,⁹ in which one half of the patients were dosed only 7 days or less before the birch pollen season. The difference in anti-IgE exposure before the season appears to be crucial for the greater efficacy observed in our study. This accords with other observations showing significant suppression of IgE-mediated clinical^{12,13} or in vitro¹⁴ responses after 27 to 90 days.

We believe that the additive efficacy of immunotherapy and anti-IgE reflects their complementary modes of action. Whereas SIT is an example of active immunization, the administration of anti-IgE reduces the immune response by decreasing levels of free IgE in the serum within hours to approximately 10 IU/mL.

Patients with allergic airways disease are commonly sensitized to multiple allergens.¹⁵ Polysensitized patients might have an enhanced IgE immune response, as shown by higher serum levels of total and specific IgE.¹⁶ However, SIT with multiple allergens appears to be less effective than single-allergen SIT¹⁷ because the mixture contains too many allergens for doses of the single allergens to be optimal.^{1,3} Therefore, anti-IgE is particularly useful for these patients.

The clinical response to SIT generally matures over several years.^{7,8} In the early years, when the response is incomplete, anti-IgE could form a useful adjunctive therapy. It will be of great interest to study whether the addi-

Asthma, rhinitis,
other respiratory
diseases

tive effect of treatment is maintained when the full doses of SIT have been administered for a prolonged period of, say, 3 seasons.

Should anti-IgE be chosen over conventional pharmacotherapy for combination with SIT in this subgroup of patients with SAR? As a systemic treatment, anti-IgE can be administered on a schedule of outpatient visits similar to that used for SIT, a regimen that patients might prefer to daily medication.¹⁸ Patients with symptoms over a long period of sequential seasons or with perennial exposure are likely to find continuing use of conventional medications unacceptable.^{4,19} In addition, a significant proportion of patients with SAR have inadequate symptom control despite optimal use of pharmacotherapy²⁰ (and these patients are candidates for SIT). Because SIT can result in worsening of atopic eczema, our observation of eczema lesions only in the placebo group could speak in favor of beneficial effects of anti-IgE on atopic dermatitis. Previous studies have shown a reduction of IgE-mediated early-phase and late-phase reactions 4 to 8 hours after allergen challenge.^{12,13} A further speculative reason for choosing to use anti-IgE in conjunction with SIT is that its effect of lowering levels of free IgE in the serum could help to reduce the risk of SIT-induced systemic IgE-mediated early-phase and late-phase reactions. Of course, this would not replace the need to administer SIT carefully in an appropriate setting.^{1,3} If anti-IgE is protective in decreasing reactions to SIT, it might have a potential use in enabling more patients to receive rush SIT, or it might permit allergists to use higher doses of SIT, inasmuch as the total allergen dose received is crucial to the efficacy of SIT. A study is planned to investigate this issue.

In conclusion, treatment with monoclonal anti-IgE antibody and SIT was more effective than immunotherapy alone and was well tolerated. This combination therapy might be a novel strategy for further reducing symptoms and additional rhinitis medication requirements in patients for whom SIT is indicated. The lack of dependence on allergen specificity makes anti-IgE especially suitable for use in polysensitized allergic patients.

REFERENCES

- WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53(44 Suppl):1-42.
- American Academy of Allergy, Asthma & Immunology. The Allergy Report. Milwaukee (WI): The American Academy of Allergy, Asthma & Immunology; 2000.
- Joint Task Force. Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol* 1996;98:1001-11.
- Norman PS. Immunotherapy: past and present. *J Allergy Clin Immunol* 1998;102:1-10.
- Durham SR, Walker SM, Varga E-M, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
- Greineder DK. Risk management in allergen immunotherapy. *J Allergy Clin Immunol* 1996;98:S330-S334.
- Walker SM, Varney VA, Gaga M, Jacobson MR, Durham SR. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. *Allergy* 1995;50:405-13.
- Bousquet J, Becker WM, Hejjoui A, Chanal I, Lebel B, Dhivert H, Michel FB. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 1991;88:43-53.
- Ädelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;106:253-9.
- Milgrom H, Fick RB, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341:1966-73.
- Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:154-61.
- Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34.
- Boulet LP, Chapman KR, Côté J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;155:1835-40.
- MacGlashan DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438-45.
- Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, Marolia H, et al. NAC Manchester asthma and allergy study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin Exp Allergy* 2001;31:391-9.
- Bousquet J, Hejjoui A, Becker WM, Cour P, Chanal I, Lebel B, et al. Clinical and immunologic reactivity of patients allergic to grass pollens and to multiple pollen species. I. Clinical and immunologic characteristics. *J Allergy Clin Immunol* 1991;87:737-46.
- Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
- Norman PS. Is there a role for immunotherapy in the treatment of asthma? Yes. *Am J Respir Crit Care Med* 1996;154:1225-6.
- Adkinson NF. Immunotherapy for allergic rhinitis. *N Engl J Med* 1999;341:522-4.
- White P, Smith H, Baker N, Davis W, Frew A. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clin Exp Allergy* 1998;28:266-70.

APPENDIX

In addition to the authors, the members of the Omalizumab Rhinitis Study Group were B. Albrecht, Marien-Hospital Wesel, Wesel; P. Bartels, Children's Hospital TU Muenchen, Muenchen; H. Bartz, University Children's Hospital, Bochum; W. Bohnet, University Children's Hospital, Freiburg; C. Bollrath, Marien-Hospital Wesel, Wesel; H. Döhmen, Aachen; T. Feuchtinger, University Children's Hospital, Bochum; F. Friedrichs, Aachen; B. Gerstner, Children's Hospital Charité-Virchow-Klinikum, Berlin; A. Gruebl, Children's Hospital TU Muenchen, Muenchen; E. Hamelmann, Children's Hospital Charité-Virchow-Klinikum, Berlin; S. Heck, Children's Hospital University of Mainz, Mainz; H. J. Heßler, Rendsburg; S. van Koningsbruggen, Children's Hospital University of Cologne, Köln; M. Kopp, University Children's Hospital, Freiburg; K. Kötz, Children's Hospital Charité-Virchow-Klinikum, Berlin; L. Lange, Children's Hospital University of Cologne, Köln; University Children's Hospital, Dresden; F. Loetzbeyer, Children's Hospital TU Muenchen, Muenchen; P. R. Mikloweit, P. Pfister, Novartis AG Basel; V. Rauls, Auguste-Viktoria Klinik, Bad Lippspringe; J. Reichenbach, Children's Hospital Medical Center, University, Bonn; F. Riedinger, University Children's Hospital, Freiburg; C. Rieger, University Children's Hospital, Bochum; E. Rietschel, Children's Hospital University of Cologne, Köln; H. Scherf, Berlin; H. J. Seeber, Grossschirma; A. Seidel, University Children's Hospital, Freiburg; V. Wahn, Schwedt/Oder; B. Wille, Schwedt/Oder; and W. J. U. Zachgo, Geesthacht, Children's Hospital Medical Center, University, Bonn (all cities are in Germany except Basel, which is in Switzerland).