

Omalizumab Improves Asthma-Related Quality of Life in Children With Allergic Asthma

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ABSTRACT. *Background and Objective.* Omalizumab is a recombinant, humanized, monoclonal anti-immunoglobulin E (IgE) antibody, developed for the treatment of IgE-mediated diseases. In children with allergic asthma, it was shown to reduce the requirement for inhaled corticosteroids while protecting against disease exacerbation. Here we report the effects of treatment with omalizumab on asthma-related quality of life (AQoL) in children with allergic asthma.

Methods. This evaluation was part of a previously reported 28-week, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of omalizumab (at least 0.016 mg/kg/IgE [IU/mL] per 4 weeks) in children with allergic asthma who were well controlled on daily treatment with inhaled corticosteroids. Dosage of beclomethasone dipropionate was kept constant for 16 weeks (steroid-stable phase), then reduced over 8 weeks to the minimum effective dose (steroid-reduction phase). This dose was then maintained for the final 4 weeks. The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was administered at baseline, week 16, and week 28.

Results. Baseline demographics, PAQLQ scores, and other data were comparable for the 2 treatment groups. At the end of the steroid-reduction phase, patients in the omalizumab-treated group reported significant improvements in the "activities" and "symptoms" domain scores as well as overall AQoL compared with placebo. More patients in the omalizumab group achieved clinically relevant (≥ 0.5) changes in PAQLQ scores during the course of the study, and this difference was significant for activities and overall AQoL.

Conclusion. Omalizumab improves AQoL in children with allergic asthma. *Pediatrics* 2002;110(5). URL: <http://www.pediatrics.org/cgi/content/full/110/5/e55>; *allergic asthma, IgE, omalizumab, children, quality of life, asthma.*

ABBREVIATIONS. QoL, quality of life; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; IgE, immunoglobulin E; AQoL, asthma-related quality of life; BDP, beclomethasone dipropionate.

Asthma can impair patient functioning not only in terms of symptoms, but also in terms of activity limitation, sleep impairment, and emotional functioning.¹ Furthermore, patients with allergic asthma are often troubled by the concomitant symptoms of other atopic disorders, particularly allergic rhinitis.² The traditional spirometric assessments (eg, forced expiratory volume in 1 second) do not measure the combined impact of these conditions on the patients' quality of life (QoL). The frequency and severity of exacerbations and the number of times an asthma patient is hospitalized for serious exacerbations are other clinically relevant factors affecting QoL that are not recorded by purely spirometric assessments. Use of the validated Pediatric Asthma Quality of Life Questionnaire (PAQLQ) could provide a more sensitive and comprehensive approach to the assessment of asthma, incorporating all of these elements and providing a clearer picture of the individual patient's overall disease status.¹

Nearly 90% of children with allergic diseases have positive skin tests to a common aeroallergen (eg, house dust mite, *Alternaria*, cockroach, cat, dog), indicating the presence of raised levels of circulating immunoglobulin E (IgE).³⁻⁷ Omalizumab (Xolair; Genentech, San Francisco, CA) is a recombinant humanized monoclonal anti-IgE antibody that forms complexes with circulating free IgE and prevents it from binding to high-affinity receptors on effector cells, thereby inhibiting allergen-induced activation.⁸⁻¹⁰ It has been reported that subcutaneous treatment with omalizumab reduces the requirement for inhaled corticosteroids while protecting against disease exacerbation in a large placebo-controlled trial in children with moderate-to-severe allergic asthma.¹¹ Here we report the findings of the effect of omalizumab on asthma-related quality of life (AQoL), which was evaluated during the latter clinical trial.

METHODS

Study Design and Patients

These QoL analyses were conducted as part of a multicenter, 28-week, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of omalizumab in children with allergic asthma,¹¹ whose asthma was well controlled with inhaled corticosteroids.

Briefly, the study enrolled male and female patients, aged 6 to 12 years, with a diagnosis of allergic asthma of at least 1 year in duration, with total serum IgE levels between 30 and 1300 IU/mL and a positive skin-prick test to at least 1 common aeroallergen

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(*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach, dog, or cat).

Eligible subjects began a 4- to 6-week run-in period in which they were all switched from their current inhaled corticosteroid to beclomethasone dipropionate (BDP). The dose was subsequently adjusted to establish the lowest dose required for an acceptable level of asthma control. This dose was maintained for 4 weeks (baseline) before entering the double-blind portion of the study.

Subjects were randomized to subcutaneous treatment with either omalizumab or placebo every 2 or 4 weeks (at least 0.016 mg/kg/IgE [IU/mL] per 4 weeks) for 28 weeks. The baseline dose of concomitant BDP was maintained during the first 16 weeks of the study (steroid-stable phase). In the next 12 weeks (steroid-reduction phase), the BDP dose was reduced by 25% every 2 weeks for the first 8 weeks until the lowest dose required for asthma control was achieved. This dose was maintained for the last 4 weeks of the study period. Patients were allowed to use albuterol as needed throughout the study.

QoL Assessment

The Pediatric Asthma Quality of Life Questionnaire (PAQLQ), developed by Juniper and colleagues¹ was used to assess the effects of asthma and its treatment on AQoL in this study. The PAQLQ is an asthma-specific QoL questionnaire designed to measure the impact of asthma on children's daily lives. The PAQLQ contains 23 questions (items) in 3 categories (domains): activity limitations (5 items), symptoms (10 items), and emotional function (8 items). All patients answered the questions using a 7-point scale to record their level of impairment in the previous 2 weeks, where 1 = maximum impairment and 7 = no impairment. The lower the PAQLQ score, therefore, the greater the impairment of AQoL.

The PAQLQ was administered 3 times during the study: at treatment baseline (week 0), at the end of the steroid-stable treatment phase (week 16), and at the end of the steroid-reduction phase (week 28).

Statistical Analysis

Differences between treatment groups were evaluated using the Cochran-Mantel-Haenszel (van Elteren) test, stratified by treatment schedule. The primary unit of analysis was the mean change from baseline scores for each domain to the end of the steroid-stable and steroid-reduction phases. Differences were considered statistically significant at the 0.05 level (2-sided). Scores of the last completed questionnaire were used (last-observation-carried-forward approach) for patients who dropped out during the study.

It was important to assess the clinical relevance of the AQoL changes demonstrated in this study. For the PAQLQ, a mean change in score of ≥ 0.5 per item has been shown to be the minimal clinically important difference.¹² The Fisher exact test was used to compare treatment groups by the percentage of patients achieving

≥ 0.5 unit improvements in their PAQLQ scores for each of the domains and for the overall PAQLQ score.

RESULTS

Demographics

Demographic information for the overall study population is shown in Table 1. A total of 334 patients were randomized in this study (225 for omalizumab, 109 for placebo). Gender, race, age, and clinical baseline measures, including mean PAQLQ domain and overall scores, were comparable between the treatment groups. Sixteen (7.1%) omalizumab and 12 (11.0%) placebo patients did not complete the study. Withdrawal of consent was the most frequent reason for premature study withdrawal in both the omalizumab (3.1%) and placebo (4.6%) groups. One patient in each treatment group discontinued participation, owing to lack of drug efficacy, and 1 patient in each group withdrew as a result of adverse events (urticaria in 1 omalizumab-treated patient, hip fracture in 1 placebo patient).

AQoL

Baseline PAQLQ scores reflected minimal impairment in AQoL. Both treatment groups showed modest improvements from baseline in PAQLQ scores during the course of the study. For within-treatment improvements, for both time periods (end of steroid-stable phase, end of study), omalizumab reached statistical significance for all domains (activities, emotions, symptoms) as well as for the overall score. Placebo reached statistical significance in the emotions domain at the end of both phases and statistical significance in the overall score only at the end of the steroid-stable phase.

For between-treatment improvements, omalizumab showed larger improvement over placebo in all domains at the end of the stable steroid phase, although the difference was not statistically significant for any domain. At the end of the study, however, omalizumab-treated patients experienced statistically significantly greater improvements from

TABLE 1. Summary of Demographics and Baseline Characteristics by Treatment (All Randomized Patients)

	Omalizumab <i>n</i> = 225	Placebo <i>n</i> = 109
Sex, <i>n</i> (%)		
Male	158 (70.2)	73 (67.0)
Female	67 (29.8)	36 (33.0)
Race, <i>n</i> (%)		
Caucasian	168 (74.7)	86 (78.9)
Black	38 (16.9)	14 (12.8)
Other	19 (8.4)	9 (8.3)
Mean age, <i>y</i> (range)	9.4 (5–12)	9.5 (6–12)
Mean duration of asthma, <i>y</i> (range)	6.1 (1–12)	6.1 (1–12)
Mean BDP dose, $\mu\text{g}/\text{day}$ (range)	284 (168–672)	267 (168–504)
Mean serum total IgE (range) (IU/mL)	348 (20–1269)	323 (29–1212)
Mean FEV ₁ , % predicted (range)	84 (49–129)	85 (43–116)
Mean PAQLQ domain scores		
Activities	4.9	4.9
Emotions	5.8	5.7
Symptoms	5.6	5.4
Overall score	5.5	5.4

FEV₁ indicates forced expiratory volume in 1 second.

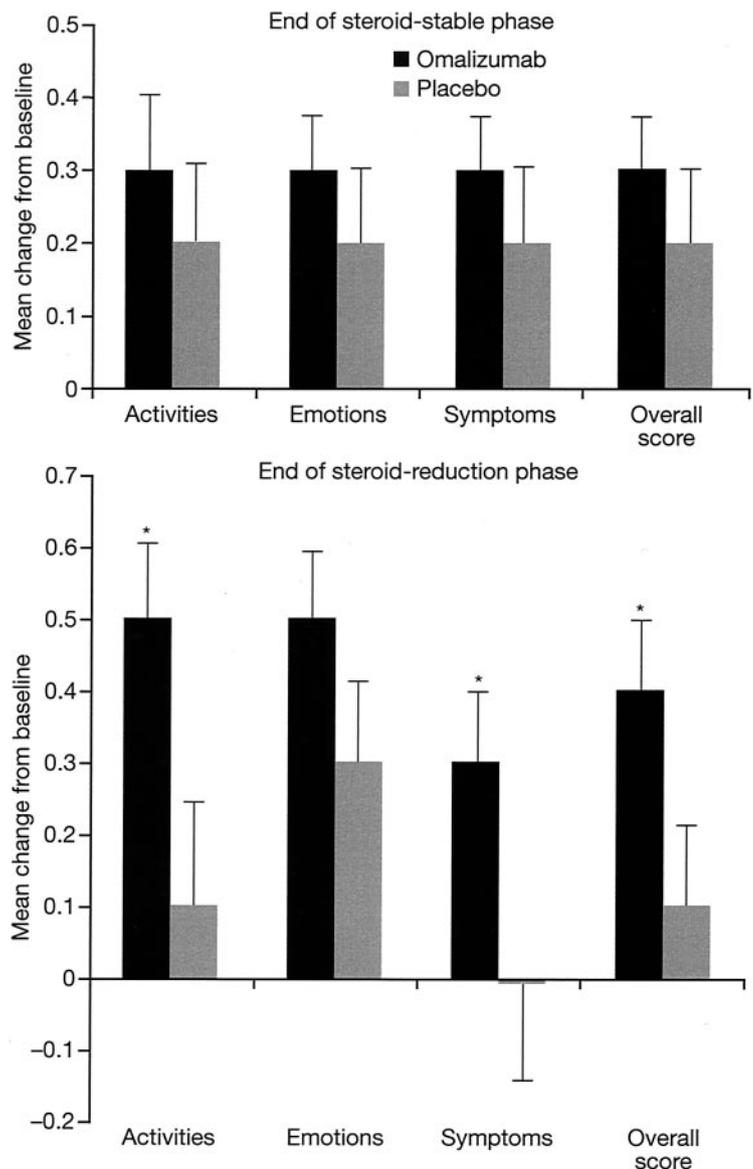


Fig 1. Mean change from baseline in PAQLQ scores during treatment with omalizumab or placebo in children with allergic asthma. * $P < .05$ versus placebo.

baseline in the activities and symptoms domains as well as the overall score compared with placebo-treated patients (Fig 1). Likewise, at the end of the study, a greater proportion of patients in the omalizumab group achieved a clinically relevant improvement in the asthma-related QoL (defined as an increase >0.5 points) than in the placebo group, reaching statistical significance for the activities domain and the overall asthma-related QoL score (Fig 2). When considering a large improvement in AQoL (defined as an increase >1.5 points), the difference between the omalizumab-treated and placebo-treated groups was particularly marked for activities (23.3% vs 14.0%, respectively; $P = .995$), symptoms domain (16.0% vs 9.3%, respectively; $P = .1814$), and overall score (13.7% vs 8.1%, respectively; $P = .2258$).

DISCUSSION

QoL assessment provides additional information that augments the traditional efficacy and safety data in clinical studies of asthma. In this study, we used the PAQLQ,¹ a rigorous questionnaire that was spe-

cifically designed to be sensitive to small, within-subject changes in AQoL over time. One unique feature of the PAQLQ is that the patients themselves select 3 of the activity limitation items. This feature may enhance content validity and can help improve the relevance of the questionnaire in clinical practice. With this questionnaire an increase in domain or overall score of ≥ 0.5 points indicates a clinically relevant improvement in AQoL.¹² This analytical approach allows a meaningful interpretation of the effect of therapeutic intervention on AQoL overall and in age-specific subgroups of children (7–17 years of age).¹

It has been reported that omalizumab reduces the requirement for corticosteroid therapy while protecting against disease exacerbation in children with allergic asthma.¹¹ The present findings show that these changes are paralleled by significant improvements in AQoL. The lack of significant differences between treatments during the steroid-stable phase was not surprising, because the patients' asthma was well controlled at baseline, and PAQLQ scores indicated

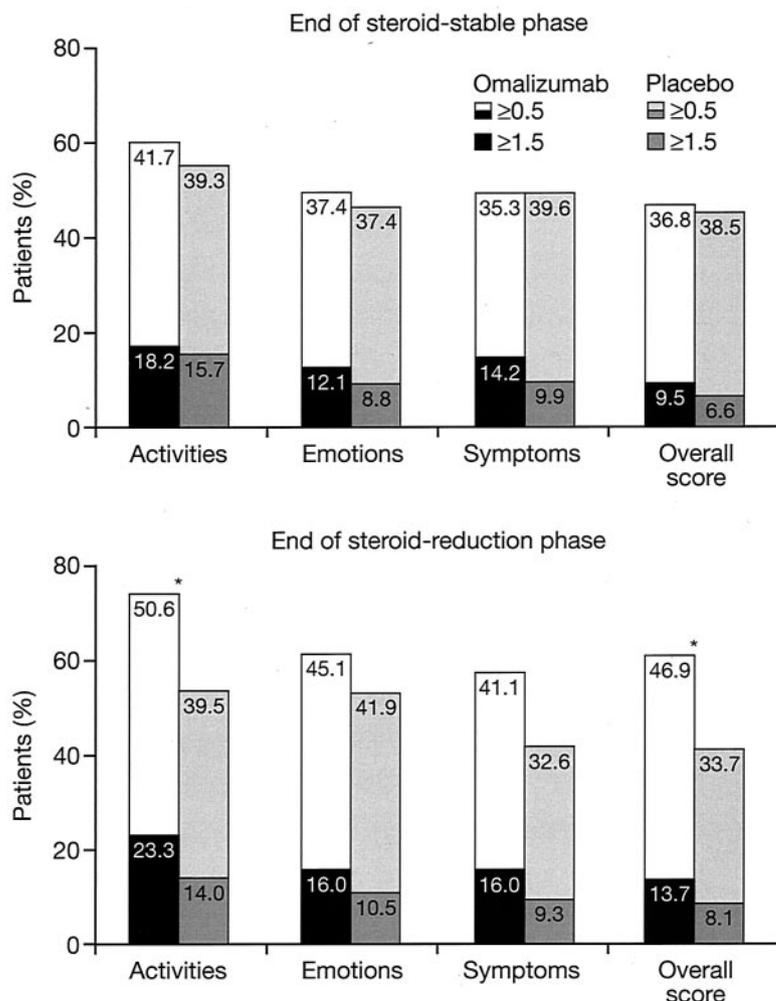


Fig 2. Percentage of patients achieving a clinically important (defined as an increase in score of ≥ 0.5 points from baseline) or large (defined as an increase in score of ≥ 1.5 points from baseline) improvement in PAQLQ scores during treatment with omalizumab or placebo in children with allergic asthma. * $P < .05$ versus placebo.

that they were relatively untroubled by their disease, leaving little room for improvement. At the end of the steroid-reduction phase, however, changes from baseline in “activities” and “symptoms” domain scores as well as overall AQoL were significantly higher for omalizumab than placebo. Furthermore, the percentage of patients achieving a clinically relevant improvement in overall AQoL was significantly higher in the omalizumab group than in the placebo group. The clinically relevant improvements in AQoL with omalizumab were achieved at the same time as a significant concomitant reduction in reliance on inhaled corticosteroids: the median dose reductions were 100% for children on omalizumab and 67% on placebo, and BDP was withdrawn completely in 55% of omalizumab-treated patients and 39% of the placebo group.¹¹ This provides compelling evidence that omalizumab targets a cause of the underlying allergic disease. Although children in the placebo-treated group reduced their corticosteroid consumption, they also used more rescue medication in the steroid-reduction period than did children who received omalizumab. Hence, because these children may have relied heavily on rescue medication to control symptoms ordinarily controlled by corticosteroid therapy, the data would seem to report a high median reduction of steroid in this group.

This may also explain the positive response of placebo-treated patients in the quality of life variables.

CONCLUSION

The results of the present study indicate that omalizumab treatment is associated with clinically meaningful improvements in AQoL in children with allergic asthma. These AQoL improvements, in this already well-controlled patient population, parallel earlier findings of enhanced disease control, although there was a significant reduction in inhaled corticosteroid consumption during omalizumab therapy.¹¹ The improvements in AQoL are also reflected in the finding that children treated with omalizumab had fewer school days missed as a result of their asthma during the double-blind treatment period ($P = .04$ vs placebo).¹¹ Likewise, significantly fewer children treated with omalizumab experienced exacerbations during the steroid-reduction phase of the double-blind treatment period than those treated with placebo ($P < .001$ vs placebo). No children in the omalizumab-treated group were hospitalized; 5 children in the placebo-treated group required hospitalization for serious asthma exacerbations.¹¹ With convenient subcutaneous administration every 2 or 4 weeks by their attending physician, treatment with omalizumab may overcome the potential for poor

compliance with anti-asthma therapy in children. Taken together, such findings confirm that omalizumab is a promising new agent for the treatment of allergic asthma.

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