resources. Other endpoints were measured, including symptoms during the 3 days preceding an attack and during the 12-day treatment period, percentage of asthma-free days, and use of \( \beta \)-agonist.

RESULTS. Almost 600 patients were randomized to each treatment arm. Almost 75% of patients had at least 1 episode of asthma, with almost half of patients culminating in an exacerbation. No significant difference was seen between groups in the number of episodes leading to asthma exacerbations. Daily montelukast reduced symptoms over the 12-day treatment period of asthma episodes compared with placebo \((P = .045)\). \( \beta \)-Agonist use was reduced with both daily \((P = .048)\) and intermittent \((P = .028)\) montelukast compared with placebo. However, because of prespecified rules for multiplicity adjustments (requiring a positive primary endpoint), statistical significance for secondary endpoints could not be concluded.

CONCLUSIONS. The number of asthma episodes leading to asthma exacerbations over a yearlong period in these young pediatric patients was not reduced by montelukast use, although improvements occurred in some endpoints.

REVIEWER COMMENTS. The treatment of pediatric patients with severe intermittent asthma is challenging for clinicians. The optimal treatment for these patients is unknown; studies do not show benefits of preventive medications as in other forms of persistent asthma. This study did not show improvement in the number of asthma exacerbations requiring utilization of health care resources with the use of montelukast, although some secondary endpoints were suggestive. The need exists for further studies to improve the prevention of the morbidity seen during the asthma exacerbations of these patients.

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Lansoprazole for Children With Poorly Controlled Asthma: A Randomized Controlled Trial


PURPOSE OF THE STUDY. To study the efficacy of proton pump inhibitor (PPI) therapy over 24 weeks in reducing symptoms in asthmatic children without symptomatic gastroesophageal reflux (GER) who had poor asthma control.

STUDY POPULATION. Subjects were between 6 and 17 years old with physician-diagnosed asthma and “labile airways function” defined as (1) 12% or greater increase in postbronchodilator forced expiratory volume in 1 second (FEV\(_1\)), (2) methacholine PC20 less than 16 mg/mL, or (3) positive exercise challenge with a 20% or greater decrease in FEV\(_1\).

METHODS. This is a multicenter, randomized, double-masked, placebo-controlled parallel clinical trial in children with asthma. All subjects were on stable doses of inhaled corticosteroids and had poor asthma control defined by study specific criteria. Subjects were excluded if they self-reported any symptoms of GER requiring treatment with a PPI or other reflux medication. The primary outcome was change in asthma control questionnaire score at the 24-week visit. Secondary outcomes included rate of acute episodes of poor asthma control, change in Asthma Symptom Utility Index, change in Asthma Control Test, change in asthma-specific quality of life for children score, methacholine PC20, spirometry, FeNO, gastrointestinal symptoms, and nocturnal awakenings. Esophageal pH studies were performed before randomization in a subset. Participating children were randomly assigned to receive lansoprazole dosed by weight.

RESULTS. One hundred forty-nine children were randomized to lansoprazole therapy and 157 were randomized to placebo. Mean age at randomization was 11 years in both groups. More than 88% of participants completed the study. Of 115, 49 (43%) 24-hour pH probe studies demonstrated abnormal esophageal acid exposure. Gastrointestinal symptom scores were not different between patients with normal versus abnormal pH studies. No differences were seen in initial prebronchodilator FEV\(_1\) or forced vital capacity in those with normal or abnormal pH studies. At week 24 of therapy, mean Asthma Control Questionnaire score had decreased by <0.5 (the predetermined clinically important difference) in both groups and was not statistically different between the 2 groups \((P = .12)\). There were no statistically significant treatment effects for any of the secondary outcome measurements. In a subanalysis of the children with abnormal pH probe studies \((n = 49)\), there was no significant effect of lansoprazole treatment for 24 weeks on any of the study outcomes. Adverse event monitoring showed treatment with lansoprazole was associated with statistically greater prevalence of upper respiratory tract infection, sore throat, and bronchitis. Activity-related bone fractures were seen in 6 of 149 lansoprazole-treated subjects and 1 of 157 placebo-treated children \((P = .06)\).

CONCLUSIONS. In children 6 to 17 years old with mild or moderate persistent asthma on inhaled corticosteroids, without GER symptoms, abnormal pH probe diagnostic of GER disease is present in 43%. Yet 24-week treatment with lansoprazole had no significant effect on measures of asthma control, quality of life, lung function, or bronchial responsiveness compared with placebo in the total group and in the subgroup of patients with abnormal pH probe studies. Increased adverse events, upper
Omalizumab and the Risk of Malignancy: Results From a Pooled Analysis

PURPOSE OF THE STUDY. Omalizumab, a humanized anti-IgE monoclonal antibody, is an approved treatment for severe persistent asthma in patients 12 years or older. Previous pooled data showed an increased number of malignancies in treated patients compared to control subjects (0.5% vs 0.2%, respectively). This study reexamined the malignancy risk from the use of omalizumab.

STUDY POPULATION. Sixty-seven phase I to IV clinical trials sponsored by the medication’s manufacturers and their extension periods were pooled for analysis.

METHODS. Studies were categorized as randomized, double-blind, placebo-controlled (RDBPC, 32/67), controlled clinical trials (40/67), or all clinical trials. Patients with a prior history of malignancy were included in 11 trials. A global safety database maintained by the manufacturer was also used to identify any omalizumab-treated patients with events that occurred after the clinical trials ended and after last exposure during a clinical trial (ARGUS). Potential malignancies (including cysts, polyps, and nevi) were identified and then blindly screened by 2 physicians with exclusion of events deemed benign by both. The remaining cases were blindly reviewed by an independent oncology panel. Cases of “definite” and “possible” malignancy were included.

RESULTS. There were 11,459 patients in all clinical trials (7789 on omalizumab/5800 patient-years; 3670 placebo-treated patients/2168 patient-years), 9424 in controlled trials (6246 on omalizumab/2978 patient-years; 3178 placebo-treated patients/2168 patient-years), and 7432 in RDBPC trials (4254 on omalizumab/2144 patient-years; 3178 placebo-treated patients/1689 patient-years). Across all clinical trials and the ARGUS database, 177 patients had 209 potential malignancies identified. After the blinded review, 56 patients (43 omalizumab-treated and 13 control patients) had a total of 62 malignancies. Twelve of the 56 patients were identified from the ARGUS database (11 omalizumab, 1 control). In the RDBPC trials (including events identified from the ARGUS database), malignancies were identified in 14 omalizumab-treated patients and 11 placebo-treated subjects (4.14 and 4.45/1000 patient-years, respectively; rate ratio = 0.93). When patients identified from the ARGUS database were excluded and only events recorded during the RDBPC trials were considered, the rate ratio for malignancy in omalizumab versus control subjects was 0.73. When all trials were examined, the incidence rates of malignancy were similar but the corresponding rate ratios were 1.35 and 1.13, respectively. The time from study entry to malignancy diagnosis was the same in treated and control patients. The dose and duration of omalizumab treatment did not affect the malignancy rate.

CONCLUSIONS. There is no association between omalizumab treatment and risk of malignancy in patients with severe persistent asthma.

REVIEWER COMMENTS. This study provides reassurance about the long-term safety of omalizumab.

IMMUNOTHERAPY
A Novel Approach in Allergen-Specific Immunotherapy: Combination of Sublingual and Subcutaneous Route

PURPOSE OF THE STUDY. To compare the efficacy and safety of a novel combination of subcutaneous immunotherapy (SCIT) for induction and sublingual immunotherapy (SLIT) for maintenance, to immunotherapy via a single method (either SCIT or SLIT) for both induction and maintenance.

STUDY POPULATION. Investigators enrolled 60 children, aged 5 to 12 years, monosensitized to house dust mite (HDM), who had been followed at a pediatric allergy immunology clinic in Istanbul for mild persistent to moderate asthma or rhinitis, with persistent symptoms despite inhaled or intranasal steroids for 2 years.
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