

The Beneficial Effects of Xolair® (Omalizumab) as Add-On Therapy in Patients with Severe Persistent Asthma who are Inadequately Controlled Despite Best Available Treatment (GINA 2002 step IV) – The Israeli Arm of the INNOVATE Study

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Abstract

Background: Patients with severe persistent asthma despite GINA 2002 step 4 treatment are at risk for asthma-related morbidity and mortality. This study constitutes the Israeli arm of the international INNOVATE study.

Objectives: To determine the efficacy and safety of Xolair® as an add-on treatment in patients with severe persistent asthma.

Methods: Asthma patients (age 12–75 years) not controlled with high dose inhaled corticosteroids and long-active beta-2 agonists were randomized to receive either Xolair® or placebo for 28 weeks in a double-blind study in two Israeli centers.

Results: Thirty-three patients, 20 females and 13 males, mean age 54 ± 11.7 years, were included in the Israeli arm of the INNOVATE study. There were neither major adverse events nor withdrawals from the study. Xolair® (omalizumab) significantly reduced the rate of clinically significant asthma exacerbations (55% reduction) and all asthma-related emergency visits (53% reduction).

Conclusions: In patients with severe persistent difficult-to-treat asthma, despite regular treatment with LABA and inhaled corticosteroids (GINA 2002 step 4), Xolair® is a safe and effective treatment.

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Asthma is a chronic inflammatory airways disease characterized by increased responsiveness of the bronchi to various stimuli, which are mainly allergenic [1]. It is an episodic disease with acute exacerbations followed by symptom-free periods [2]. These exacerbations are associated with patients' limited activity and reduced quality of life, as well as emergency room visits or hospitalizations. The prevalence of asthma and mortality caused by asthma is constantly increasing [3]. About 5% of asthma patients have severe persistent disease which is inadequately controlled by treatment with inhaled corticosteroids or long-acting beta-2 agonists [4]. Oral corticosteroids are beneficial in these patients but its prolonged usage may lead to severe adverse events [2]. These patients, classified as GINA (Global Initiative for Asthma) 2002 step 4 stage [5], are at high risk for repeated hospitalizations and mortality [2].

Immunoglobulin E plays a major role in the pathogenesis of asthma [6]. Upon exposure to a sensitizing aeroallergen, the

latter causes cross-linking of IgE that is present on mast cells in the tracheobronchial tree, leading to degranulation of allergic and inflammatory mediators. These mediators cause airway hyper-responsiveness and bronchospasm [7]. IgE may also facilitate asthma via other immune mechanisms such as up-regulation of dendritic cell function (antigen presentation) or by B cell stimulation via the low affinity receptor for IgE (FcεRIIs) [8].

Xolair® (omalizumab) is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds IgE of the exact same epitope on the Fc region which binds to the IgE receptor [9]. Thus, Xolair® binds to free IgE, and cannot bind or interact with IgE that is already bound to mast cells or basophils. Therefore, Xolair is not anaphylactogenic. It binds only to free IgE, regardless of antigenic specificity, forming complexes of IgE-Anti-IgE with significant (up to 99%) reduction of circulating free (not bound to Xolair®) IgE levels [10]. Previous studies have reported the beneficial effects of Xolair® in the treatment of asthma and allergic rhinitis [11–13].

The INNOVATE study (**I**Nvestigation of **O**malizumab in **s**e**V**ere **A**sthma **T**r**E**atment) is a randomized placebo-controlled double-blind study of 419 patients with severe persistent asthma who were inadequately controlled despite GINA 2002 step 4 therapy [14,15]. Xolair® was given as an add-on therapy. We report here the results of the Israeli arm (33 patients) of the INNOVATE study.

Patients and Methods

Patients

The study participants were patients with severe persistent ("difficult-to-treat") asthma. The inclusion criteria were: age 12–75 years; severe-persistent symptomatic asthma despite regular treatment with inhaled corticosteroids > 1000 µg/day of beclomethasone dipropionate (or equivalent) and LABA (GINA 2002 step 4 treatment); forced expiratory volume in the first second between 40% and 80% of predicted normal value with 12% reversibility in response to salbutamol inhalation; two or more asthma exacerbations resulting in emergency room visit/hospitalization in the previous year despite GINA step 4 treatment; positive skin-prick test to one or more relevant aeroallergens; and total IgE levels of 30–700 IU/ml. Regular therapy (more than 4 weeks before

LABA = long-active beta-2 agonists

randomization) with theophylline, oral β_2 -agonists, montelukast (Singulair®) and up to 20 mg/day of prednisone were permitted. Excluded from the study were smokers, patients who were not able to sign an informed consent according to Good Clinical Practice rules, patients who were treated for asthma exacerbations within 4 weeks prior to the randomization, treated with an immunomodulator (e.g., methotrexate, cyclosporine) within 3 months of the first visit, or treated previously with Xolair®. The study was approved by the institutional Helsinki committee.

Study design and endpoints

The present study was a randomized placebo-controlled double-blind study with a 7 day screening period followed by a "run-in" period of 4 weeks for adjusted best treatment and another 4 weeks with no other change in asthma treatment. Then, a 1:1 (Xolair®: placebo) randomization was conducted followed by 28 weeks of an add-on (Xolair®/placebo) drug treatment period.

The primary endpoint was the rate of clinically significant asthma exacerbation (defined as worsening of symptoms requiring systemic steroids treatment) during the 28 weeks "drug-on" period. In addition, hospitalizations, emergency room and unscheduled physician visits were recorded. Spirometry was performed at each visit, quality of life was assessed using the Juniper questionnaire, and asthma clinical symptom score and the usage of rescue medications were recorded in diary reports [14]. The diary reports were twice daily recordings made by each patient on an electronic device (Palm computer) and included daily symptoms, peak expiratory flow and medications; the computer generated a score that was transmitted by a modem to the main study computer. All adverse effects were recorded throughout the study.

Xolair® (omalizumab) dosage was based on both body weight and total serum IgE levels (0.016 mg/kg per 1 IU/ml IgE). Xolair® was given by subcutaneous injection every 2–4 weeks; the maximum dose of a single injection was 300 mg, thus higher doses (> 300 mg) were injected every 2 weeks rather than every 4 weeks.

Results

The Israeli arm of the INNOVATE study was performed in two medical centers – Hadassah (Jerusalem) and Kaplan (Rehovot). A total of 33 patients were randomized to the study (Hadassah 17, Kaplan 16); all of them completed the study and there were no withdrawals. The mean age of the study patients was 54 ± 11.7 years. There were 20 females (60.6%) and 13 males (39.4%) with a mean duration of asthma before study entry of 27.4 ± 15.4 years. Total serum IgE in our patients at study entry was 178.7 ± 141.7 IU/ml. The mean FEV1 (% of predicted) was 55.6 ± 15.6 with a mean reversibility of $16.8 \pm 10.8\%$. As shown in Table 1, all our patients were treated with high doses of inhaled corticosteroids and LABA (GINA 2002 step 4 treatment). A relatively high proportion of our 33 patients (33%) were also treated with daily oral corticosteroids.

The rate of clinically significant asthma exacerbations during

FEV1 = forced expiratory volume in the first second

Table 1. Demographic and background characteristics of the Israeli and INNOVATE patients

	INNOVATE patients (n=419)	Israeli patients (n=33)
Age (yrs), mean (SD)	43.3 (13.4)	54 (11.7)
Gender, n (%) female	279 (66.6)	20.0 (60.6)
Duration of asthma, mean (SD)	23.0 (15.0)	27.4 (15.4)
IgE (IU/ml), mean (SD)	193.6 (149.1)	178.7 (141.7)
FEV1 (% predicted), mean (SD)	61.3 (14.1)	55.6 (15.9)
FEV1 (% reversibility), mean (SD)	26.7 (23.4)	16.8 (10.8)
Inhaled corticosteroids (µg/day), mean (SD)	2330 (1099)	2230 (640)
LABA use (%)	100	100
Daily oral corticosteroid use (%)	21.7	33
Theophylline (%)	27.4	33
Anti-leukotriene (%)	34.8	21.6

the 28 weeks "drug-on" period (defined as symptomatic exacerbations that required oral corticosteroids treatment) was adjusted to the baseline exacerbation history [14]. As demonstrated in Figure 1, the rate of clinically significant asthma exacerbations was reduced by treatment with Xolair® (33.3% vs. 61.1% for Xolair® and placebo, respectively). Moreover, Xolair® treatment dramatically reduced the rate of severe asthma exacerbations in our patients (7% vs. 33%), defined as FEV1 < 60% of personal best and the requirement for systemic corticosteroids treatment.

The rate of asthma-related emergency room visits, hospital admissions and unscheduled physician visits were all lower (about half) for Xolair®-treated patients as compared to the placebo group (13% vs. 27% for emergency room visits, 13% vs. 22% for hospital admissions, and 6% vs. 11% for unscheduled physician visits for Xolair® vs. placebo, respectively [Figure 2A-C]. As shown in Figure 3, Xolair® treatment halved (32% vs. 60%) the ratio of all emergency visits (asthma-related emergency room and unscheduled physician visits and asthma-related hospital admissions).

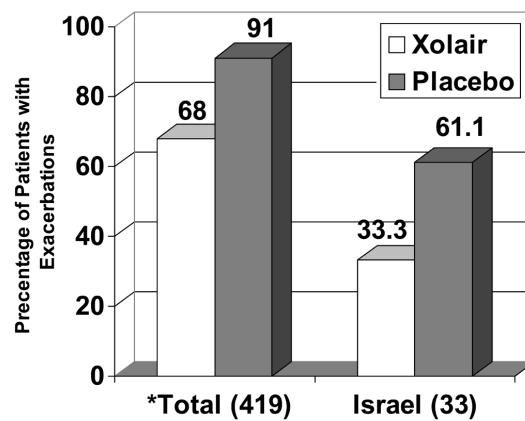


Figure 1. Clinically significant asthma exacerbations during the 28 week "drug-on" period. Clinically significant asthma exacerbations, defined as symptomatic exacerbations, required initiating or increasing the dose of systemic corticosteroids. The rate was adjusted for baseline asthma exacerbation history.
* 26% reduction, $P = 0.042$.

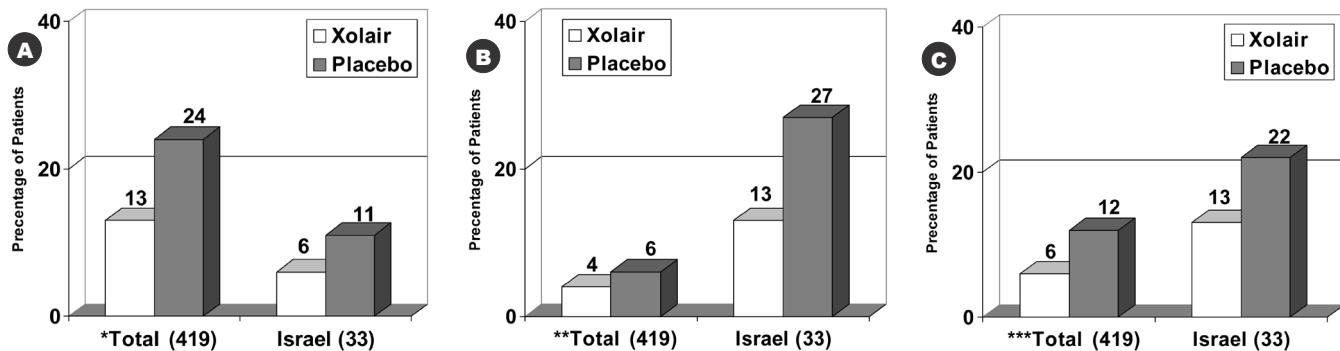


Figure 2. Emergency room, hospital admissions and unscheduled physician asthma-related visits during the “drug-on” period. Xolair® decreased the rate of asthma-related unscheduled physician visits [A], emergency room visits [B], and asthma-related hospital admissions [C].

* 46% reduction, $P = \text{not significant (NS)}$

** 33% reduction, $P = \text{NS}$

*** 50% reduction, $P = \text{NS}$.

All our patients completed the entire study and there were no dropouts or major adverse events. Two patients (one from the Xolair® and one from the placebo group) reported upper respiratory tract infections and another two (from the Xolair® group) had injection site reactions that did not require discontinuation of the drug (Xolair®).

Discussion

This study, with 33 patients, which constitutes the Israeli arm of the international INNOVATE study, clearly demonstrates the efficacy of Xolair® in “difficult-to-treat” patients with severe asthma that is not controlled despite regular treatment with high dose inhaled corticosteroids and LABA (GINA 2002 step 4 therapy). Xolair® as an add-on therapy reduced the rate of clinically significant asthma exacerbations (by about half) as well as the rate of severe asthma exacerbations and asthma-related emergency visits and admissions.

The patients who were included in the INNOVATE Israeli arm received, in addition to high dose inhaled corticosteroids and LABA, other asthma medications, including: oral corticosteroids (33%), anti-leukotriene (montelukast) (21.6%) and theophylline (33%) [Table 1]. Nevertheless, our patients were symptomatic and inadequately controlled (see inclusion criteria in the Methods section). The demographic and background characteristics of our 33 Israeli patients were similar to those of the entire INNOVATE study patients [Table 1]. Moreover, a higher proportion of our patients were treated with systemic corticosteroids (33%) and theophylline (33%) compared to the entire INNOVATE study population (21.7% and 27.4% for systemic corticosteroids and theophylline treatment respectively). Thus, the conclusions of the INNOVATE study [14,15] are applicable to our patients. Indeed, the beneficial effects of Xolair® in our arm were similar to those observed for all 419 patients who participated in the INNOVATE study [14].

The addition of Xolair® in our patients with severe uncontrolled asthma despite GINA step 4 treatment resulted in a 54.5% reduction in the number of clinically significant asthma exacerbations [Figure 1], a 21.2% reduction of severe asthma exacerbations ($\text{FEV}_1 \leq 60\%$ of personal best) and systemic cortico-

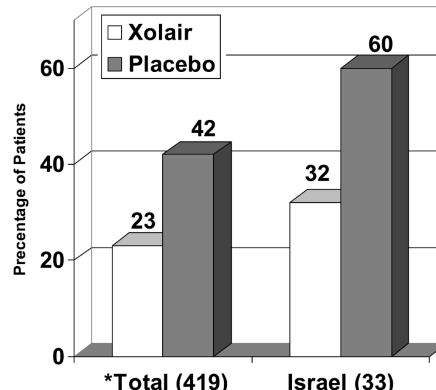


Figure 3. Total emergency visits during the “drug-on” period. Xolair® reduced, significantly, all asthma-related emergency visits (emergency room + hospital admissions + unscheduled physician visits).

* 45% reduction, $P = 0.038$.

steroids treatment), along with a reduction in all asthma-related emergency visits [Figures 2 and 3].

The reduction rate in the above parameters was comparable between the 33 Israeli patients and the entire 419 INNOVATE patient group, although the relatively small number of patients in the Israeli arm of the study did not allow for statistical evaluation.

No severe adverse events were observed in our study and all randomized patients completed the study. In the entire INNOVATE study [14], Xolair® was well tolerated and the rate of adverse events (mostly mild in severity) was similar in both the Xolair® and placebo groups. Injection site reactions were more common in the Xolair® (5.3%) than the placebo group (1.3%) [14]. It should be noted that in previous studies [16,17], cancer developed in more patients treated with Xolair® (20/4127, 0.22%) than in those treated with placebo (5/2236, 0.48%), though the difference was not statistically significant. Most neoplasms were epithelial or solid organ cancers. Recently, a post-marketing report of 39,500 asthma patients treated with Xolair® demonstrated a low rate of malignancy (0.001%). However, it should be noted

that the spontaneous reporting rate in post-marketing surveys is usually lower than that of clinical trials. Xolair® binds IgE via the binding epitope of IgE to its receptor on mast cells [6]. Thus, it should not react with IgE that is already bound to the cell surface (e.g., mast cells) and therefore Xolair® is not expected to cause anaphylaxis. Nevertheless, two patients (< 0.01%) with late anaphylactic reactions were observed a few hours after the first Xolair® injection. Although autoantibodies directed against the murine part of Xolair® can, theoretically, be generated, it appears to be extremely rare and has no clinical significance [16].

In conclusion, Xolair® is effective, safe and well tolerated in patients with uncontrolled severe asthma despite regular GINA 2002 step 4 treatment. As an add-on treatment, it reduced the number of severe asthma exacerbations and total asthma-related emergency visits and hospitalizations. Therefore, Xolair® treatment should be considered as an add-on treatment for patients with severe persistent asthma who are inadequately controlled despite high doses of inhaled corticosteroids and LABA (GINA 2002 step 4 treatment).

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