Evaluation of Xolair® (omalizumab) Therapy in Patients Treated at Örebro University Hospital 2006-2017

Author: Malin Althin, medical student
Supervisor: Lennart Nilholm, MD, Senior Consultant
Lung Clinic, Örebro University Hospital, Örebro, Sweden
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Abstract

**Background**: Xolair® is a treatment option for allergic asthma patients whose symptoms are not adequately controlled with inhaled corticosteroids and long-acting β₂-agonist bronchodilators. The treatment has been available at Örebro University Hospital’s Lung Clinic since 2006.

**Objective**: This report serves the purpose of analysing Xolair® data from real clinical practice.

**Method**: This is a retrospective non-intervention study which summarizes the treatment outcome for 38 patients who have or are receiving Xolair® treatment at the Örebro University Hospital’s Lung Clinic between 2006-2017. The analysis is conducted by using several variables divided into the sections study population characteristics, Xolair® treatment specifications, and outcome of treatment. The main variables analysed are serum IgE values, reasons for terminating treatment, adverse effects of treatment, and forced expiratory volume after 1 second (FEV₁), ratio between FEV₁ and forced vital capacity (FEV₁/FVC) and number of asthma exacerbations before and after treatment.

**Results & Conclusion**: Results of the comparison of before and after treatment values for FEV₁, FEV₁/FVC and exacerbation frequency revealed nonsignificant data. Adverse reactions to treatment was unusual, most patients followed dosage recommendations given by FASS and the most common reason for terminating treatment was because of no subjective or objective improvement in asthma symptoms with treatment.

**Abbreviations**

- **AHR**: airway hyperresponsiveness
- **APC**: antigen presenting cell
- **CD-sens**: allergen threshold sensitivity
- **FASS**: Farmaceutiska Specialiteter i Sverige (translation: Pharmaceutical Specialities in Sweden)
- **FEV₁**: forced expiratory volume measured in 1 second
- **FEV₁/FVC**: ratio between forced expiratory volume measured in 1 second and forced vital capacity
- **FVC**: forced vital capacity
- **Fc region**: fragment crystallisable region
- **FVC**: forced vital capacity
- **IgE**: immunoglobulin E
- **IL**: interleukin
- **Sd**: standard deviation
- **TGF**: transforming growth factor
- **T₈₂**: T helper type II cell

**Search words**: Xolair®, omalizumab, allergic asthma, FEV₁, FEV₁/FVC, IgE
1 Introduction

1.1 Asthma

Asthma is a chronic and heterogeneous disease with several different endotypes, characterised loosely by variable obstruction, inflammation and hyperresponsiveness in the airways [1]. The obstruction is observed clinically by the symptoms episodic breathlessness, chest tightness, wheezing, coughing and airway hyperreactivity [2–4]. The symptoms may be partly explained by airway hyperresponsiveness (AHR) defined by Murdoch et al as “ease with which the airways narrow in response to a bronchoconstrictive challenge”. Airway hyperresponsiveness culminates in an increased sensitivity and reactivity to a stimulus [2].

As for the localisation of the disease, the inflammatory process spreads from the conducting airways to the smaller airways as the disease progresses in severity and becomes chronic [1]. The prevalent localisation of the inflammation varies depending on the airway area affected, with submucosal inflammation dominating in the large airways and inflammation outside the smooth muscle tissue dominating in the smaller airways [1].

The exact etiology behind asthma is unknown, but genetic and environmental components are thought to influence the risk for developing asthma [1]. Susceptibility genes such as ADAM33 [1] have been identified but according to Lötvall et al underlying genetic links have remained evasive. One of the reasons why underlying reproducible genetic and environmental factors have been so difficult to find may be due to there being various disease variants with their respective etiologies and pathologies [5]. To compare two such asthma variants, aspirin-sensitive asthma and allergic asthma are two recognized subgroups with similar symptoms but differing triggers and, most likely, underlying pathophysiological mechanisms [5].

1.2 Allergic asthma

Allergic asthma is the most common variant of asthma [3] and characteristic of allergic asthma is a T-helper type 2 cell (Th2) response directed against an inhaled antigen in the airways [1]. The disease’s pathology can be divided into four sections: allergen sensitization in the airways, the early phase asthmatic reaction, the late phase asthmatic reaction and airway remodelling.

For an inhaled antigen to be identified by Th2 cells requires allergen sensitization, a process which begins with antigen capture by the dendritic cells which scout the airways [1]. Dendritic cells are a type of antigen-presenting cells (APCs). After processing the antigen,
APCs proceed to lymph nodes and present their findings to B and T cells [6]. With the correct interaction with co-stimulatory molecules and cytokines, Th2 cells can become activated. These activated Th2 cells secrete cytokines with several consequences; the production of allergen-specific immunoglobulin E (IgE), promotion of allergen presentation to CD4+ T cells which aids in triggering a Th2 response by dendritic cells, recruitment of eosinophils and growth of mast cells [3]. According to Cho J et al experimental evidence suggests that these allergen-specific Th2 cells and their cytokines also direct mucus hypersecretion from the airways, AHR and allergic inflammation [7]. More specifically, activated Th2 cells produce interleukins (IL-) 4, 5 and 13. IL-4 and IL-13 mediate the production of IgE by B cells and afterwards IgE is released into the circulation [6, 8]. IgE circulates until it finds the high-affinity IgE receptor, located on mast cells and basophils in tissue or blood, respectively [6].

The early phase asthmatic reaction is predominantly mediated by mast cells and starts when allergens bind to allergen-specific IgE on mast cells [1, 6]. Allergens are defined by Corry et al as having the ability to elicit a Th2 cell response and IgE production [8]. Allergen binding to IgE activates mast cells which release histamine, tryptase and other proteases, heparin and eicosanoids [1, 6]. Prostaglandin synthesis and cytokine transcription also occurs. The net result is a 30-60 minute reaction with constriction of smooth muscle in the airways, vascular leakage and mucus production [6].

The late phase starts 4 to 6 hours later and is characterized by constricting airway inflammation [6]. Both T-cells and eosinophils are given a role in maintaining this inflammation. Eosinophils are recruited from bone marrow to the airways by eotaxins 1-3 and IL-5, and contribute to the ongoing inflammation and tissue damage by releasing their own mediators [1]. Eosinophils release chemokines, cytokines, eicosanoids, basic proteins and superoxide which contribute to the inflammation’s continuation and tissue-damage in the airways [1].

Airway remodelling further contributes to increased obstruction as it causes thickening of the basement membrane and decreases the airway diameter [2]. Other airway changes include smooth muscle hyperplasia and hypertrophy, angiogenesis, mucous gland hyperplasia and a damaged epithelial barrier [1, 2]. Several mediators contribute to the remodelling. Eosinophils are thought to contribute to airway remodelling by stimulating fibrogenesis, collagen production, and myofibroblast proliferation by their release of transforming growth factor (TGF)-β1 [1].
1.3 Current Pharmacological Treatment Options for Allergic Asthma

Pharmacological treatment of asthma currently consists of bronchodilators and corticosteroid inhalators with drug dosage increasing with increasing symptoms. If symptoms cannot be adequately controlled with the use of the two previously mentioned inhalator methods, additional pharmacological treatments can be added [10]. Xolair® is one such example. Xolair® is indicated as a treatment option for patients with poorly controlled allergic asthma despite treatment with inhaled corticosteroids and inhaled long-acting \( \beta_2 \) agonist bronchodilators [11].

1.4 Xolair® (omalizumab) as a Treatment Option for Allergic Asthma

Xolair®’s active ingredient is omalizumab [12], a recombinant humanised monoclonal antibody which binds to the fragment crystallisable region (Fc) region of circulating IgE [11]. This Fc region is the target of both the high-affinity and low-affinity IgE receptors which are found on mast cells and basophils [9, 11]. By binding to the Fc region, Xolair® prevents IgE from binding to and activating the IgE receptors. This action prevents the start of the allergic cascade following allergen inhalation by inhibiting the release of inflammatory mediators from mast cells and basophils [9, 11]. When Xolair® binds to the Fc region it results in an immune complex which can be quickly eliminated from the system and, more specifically, removes IgE from the circulation [9].

Xolair® is administered by subcutaneous injection and its dosage is dependent on the patient’s weight and serum IgE levels. The dosage interval can be either 2 or 4 weeks [12]. Xolair® (omalizumab) can be administered in doses between 75 mg to 600 mg, with the highest recommended dose being 600 mg omalizumab every second week [12].

1.5 Clinical Evidence for Xolair®’s (omalizumab’s) effect on allergic asthma

Numerous reports showcase Xolair®’s effect in treating patients with allergic asthma [11, 13–16]. Evidence suggests that it can reduce IgE-mediated inflammation in the airways [11] and the number of IgE-carrying cells in the airways [11, 17]. IgE-carrying cells such as mast cells can initiate inflammation upon contact with IgE’s specific antigen or more precisely the allergen [6]. Therefore, Xolair® is also proposed to be able to decrease the early and late asthmatic response [17].

As for asthmatic symptoms, studies have also reported a decrease in the number of asthma exacerbations reported in patients [11, 13, 14] and in the use of rescue medicines [11].
Patients were also reported in one study to be able to tolerate longer allergen exposure than their placebo-treated counterparts [16].

2 Objective
The objective of this non-intervention retrospective study was to analyse the effects of Xolair® (omalizumab) in patients treated at Örebro University Hospital’s Lung Clinic between 2006 to spring 2017. The questions used to study this were if patients were following dosage recommendations, the frequency and types of adverse effects, reasons for terminating treatment, and changes in forced expiratory volume in 1 second (FEV1), number of asthma exacerbations and the ratio between FEV1 and forced vital capacity (FEV1/FVC) values after treatment. The goal of this analysis was to gain insight about Xolair® treatment in real clinical practice.

For clarification Xolair®’s active substance omalizumab will be used to denote the treatment name for the sake of consistency throughout the report.

3 Method
Patient medical records were selected from Örebro University Hospital’s Lung Clinic based on omalizumab treatment between 2006 and spring 2017. Patient medical files were reviewed and information about patient characteristics, treatment specifications, and outcome of treatment was extracted for comparison with pre-existing Xolair® data. Variables were selected beforehand and data that complied with the variables was retrieved from patient medical records and used in the study.

3.1 Study Population
The following criteria were set up for inclusion in the study; present or former Xolair® (omalizumab) treatment at Örebro University Hospital’s Lung Clinic between 2006 and spring 2017 and a diagnosis of allergic asthma at the time of the study. Patients were selected for omalizumab treatment based on poorly controlled allergic asthma symptoms despite maximum treatment with long-acting β2-agonist bronchodilators and inhaled corticosteroids.

3.2 Variables
Variables include descriptive and clinical data pertaining to characteristics of the study population, omalizumab treatment specifications and treatment outcome.

Data pertaining to the study population characteristics were selected to analyse the homogeneity and heterogeneity of the patients, including age, gender, age at asthma
diagnosis, serum IgE values, number of asthma medications prescribed, and allergens. Age was recorded on the 8th of December 2017. Medicine lists were taken from patient medical files as close to the last date of omalizumab-administration as possible. Allergens were classified according to the lung clinic’s patch test with the following categories: hazel, timothy grass, birch, mugwort, mites (D. pteronyssinus, D. farinae), mold (Alternaria sp., Aspergillus fumigatus, Cladosporium sp.) and animals (dogs, cats, horses).

Variables related to omalizumab therapy include dosage of omalizumab (mg), if the dosage was changed during treatment, reason for treatment termination, reason for re-starting treatment after termination, and treatment length. Weight and IgE levels were compared with a dosage chart retrieved from the Swedish Farmaceutiska Specialiteter i Sverige (Pharmaceutical Specialities in Sweden, FASS) to determine if dosage recommendations were followed for all patients. Treatment length was counted from the first day of omalizumab administration until treatment termination or the 8th of December 2017 for terminated and ongoing treatments, respectively.

Treatment outcome was analysed using the variables adverse effects and values for FEV1, FEV1/FVC and number of asthma exacerbations before and after treatment. FEV1 and FEV1/FVC values were extracted from spirometry tests before treatment, at approximately 4 months after treatment start, and 1 year after treatment start. FEV1 is a measurement of the maximum air volume a patient can breathe out in 1 second after drawing a deep breath. FEV1/FVC shows how much of the maximum volume the patient could exhale in one breath was exhaled in the first second. Both these values are used to measure lung function.

Information about the number of asthma exacerbations before and after treatment was also extracted from patient medical files. To be defined as an asthma exacerbation one of two criteria needed to be fulfilled; either that the asthma episode required a prescription of oral corticosteroids or antibiotics, or the asthma episode was defined by medical personnel as an exacerbation.

3.3 Statistics
Descriptive data was analysed with Microsoft Excel For Mac (Version 15.32). R: A Language and Environment for Statistical Computing (2017) was used to perform the paired t-test on exacerbations 1 year before treatment beginning and between 1-2 years after treatment start and to determine FEV1 and FEV1/FVC before and after treatment. Data with a p value under 0.05 was considered significant.
3.4 Ethical considerations
To gain insight about omalizumab, information was retrieved from the Swedish healthcare organization’s medical records system. Information such as age, occupation and treatment duration has been collected to analyse the characteristics of the study population, but these are nevertheless data that patients may be able to identify themselves from because the sample population is small. Hence from an ethical standpoint it should be acknowledged that risk for identification of study participants exists. The following steps were taken to minimize this risk: firstly, information extracted from patient medical files was kept in a password-protected Excel file which only the author had access to. Secondly, information extracted about individual patients did not include name or Swedish security/identification number. Finally, after the completion of this study, this file will be deleted.
Since this is a retrospective study, information relating to omalizumab was retrieved from complete patient medical files including information about medical visits to other clinics than to the lung clinic from 1 year before the omalizumab treatments began until the treatment ended. However, no information was collected outside of the variables outlined in the study.

4 Results
4.1 Subject characteristics
A total number of 38 patients were selected for the study as they were patients at Örebro University hospital, were receiving omalizumab-treatment for their allergic asthma and had started treatment before spring 2017. Not all 38 patients had data for every variable used in the study and since it is a retrospective study, this information was not retrieved by contacting the patients. Therefore, the study population varies between the variables. The patient sample is described more in table 1.

<table>
<thead>
<tr>
<th>Table 1: study population characteristics of the 38 patients receiving Xolair® (omalizumab) treatment at Örebro University Hospital from 2007 to spring 2017. N stands for number of patients who had data for that variable. Sd stands for standard deviation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total study population</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male (percentage of total population)</td>
</tr>
<tr>
<td>Female (percentage of total population)</td>
</tr>
<tr>
<td><strong>Median age in years (range)</strong></td>
</tr>
<tr>
<td><strong>Median BMI (range) m=male, f=female</strong></td>
</tr>
<tr>
<td><strong>Mean (sd) number of diagnoses other than allergic asthma</strong></td>
</tr>
</tbody>
</table>
Mean (sd) serum IgE  
631.2 (853.5)

Age of Asthma diagnosis* (n=26):
Childhood  
21
Adulthood  
5

Smoking history (n=37):
Never smoked  
27
Previous Smoker  
10
Current Smoker  
0

Average number (sd) of medicines prescribed to patients for allergic asthma excepting omalizumab  
3 (1.1)

* Most medical files did not give an exact age for asthma diagnosis, hence the two groups “childhood” and “adulthood” have been tentatively used. Childhood is defined as between 0-18 years of age and adulthood defined as being over 18 years of age.

The most common allergens reported were: dogs (74% of patients reactive to allergen), timothy grass (74% reactive to allergen), cats (61% of patients reactive to allergen) and birches (58% of patients reactive to allergen). Figure 1 details the allergens patients responded to and how many patients responded.

![Positive Allergen Response in Study Population](image)

Figure 1: Allergens which patients were reported to be allergic to (y-axis) and the number of patients (x-axis). Data was collected from 35 out of 38 patients.

### 4.2 Omalizumab Treatment Specifications

The average omalizumab therapy length of ongoing treatment was 841 days and for completed treatment 1,277 days. 20 patients had at the time of the study ended their treatment and 18 were still receiving omalizumab-therapy.
Of the 18 patients not following the dosage recommendations indicated by FASS, 4 had a longer interval between doses, 3 had lower dosages, 3 had a higher dosage or a shorter interval than recommended, and 5 patients had a serum IgE level higher than there were recommendations for in FASS. The other 2 patients who did not follow current treatment recommendations followed the old dosage recommendations that were replaced 3-4 years ago.

Out of the 38 patients, 24 had had lasting or brief termination of their omalizumab treatment. The most common reason was that the patient experienced no changes in symptoms and there was no clinical proof to validate therapy continuation (table 2).

**Table 2: Summary of the reasons for Xolair® (omalizumab) therapy termination. 24 out of the 38 patients in the study terminated their therapy, of which 3 patients terminated their treatment more than once.**

<table>
<thead>
<tr>
<th>Reason for terminating omalizumab treatment</th>
<th>Number of therapy terminations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No subjective/objective benefits of treatment</td>
<td>9</td>
</tr>
<tr>
<td>Attempt at withdrawal of treatment</td>
<td>6</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Negative effect of treatment on asthma symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Switch to another treatment</td>
<td>1</td>
</tr>
<tr>
<td>Patient’s own request</td>
<td>2</td>
</tr>
<tr>
<td>Unclear/Unknown</td>
<td>7</td>
</tr>
</tbody>
</table>

5 patients re-started omalizumab treatment. Their reason for re-start was because of increased asthma symptoms after termination of therapy.

28 patients had unchanging interval/dosage of omalizumab, respectively, throughout their entire treatment. Of the 10 patients who had changes in the interval/dosage, 3 changed back to their original prescription and 7 did not.

4.3 Outcome of Treatment

4.3.1 Adverse Effects Experienced with Omalizumab

Out of 38 patients that were administered omalizumab, 5 (13%) reported adverse effects, of which the most common were headaches and tiredness (Figure 2).
4.3.2 FEV1 Values Before and After Treatment

FEV1 values were collected before treatment and at approximately 4 months and 1 year after treatment start. 13 patients had FEV1 values for before treatment and after 4 months of treatment. 8 patients had FEV1 values for before and after 1 year of treatment (table 3).

Table 3: Summary of mean FEV1 values before and after treatment start with Xolair® (omalizumab). Sd stands for standard deviation. L stands for litre and n stands for number of patient’s data was collected from.

<table>
<thead>
<tr>
<th></th>
<th>Mean (sd) FEV1 before Omalizumab therapy</th>
<th>Mean (sd) FEV1 between 4-6 months after Omalizumab therapy start</th>
<th>Mean (sd) FEV1 one year after Omalizumab therapy start</th>
<th>Percent Increase before vs. after</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.71 l (1.02) (n=13)</td>
<td>2.87 l (0.91)</td>
<td>6%</td>
<td>0.094</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.40 l (0.52) (n=8)</td>
<td>2.58 l (0.41)</td>
<td>7%</td>
<td>0.094</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To examine if FEV1 values increased or decreased significantly after treatment, 2 paired t-tests were conducted. The first compared each patients’ before and after values for before treatment and after approximately 4 months of treatment. The mean of that difference had a p-value of 0.094. This reveals that changes in FEV1 values before and after treatment could not be verified as significant.

The second t-test compared each patients FEV1 values for before treatment and after 1 year of treatment. The mean difference between each patient’s before and after values that this test generated had a p-value of 0.094 which suggests that any changes in FEV1 after treatment are also nonsignificant.

Figure 2: Adverse effects reported with Xolair® (omalizumab) treatment between 2006 and spring 2017. The most commonly reported adverse effects of tiredness and headache were both reported by the same two patients.
4.3.3 FEV1/FVC Values Before and After Treatment

FEV1/FVC values used the same two previously mentioned intervals, with 13 patients having data for before treatment and approximately 4 months after treatment start. 8 patients had data before treatment and FEV1/FVC values after approximately 1 year of treatment (table 4).

Table 4: Mean of FEV1/FVC values taken from patient spirometry tests at the following time intervals; before Xolair® (omalizumab) treatment start, approximately 4 months after treatment start and approximately 1 year after treatment start. Sd stands for standard deviation.

<table>
<thead>
<tr>
<th>Mean (sd)</th>
<th>Mean (sd)</th>
<th>Mean (sd)</th>
<th>Percent increase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC before Omalizumab therapy</td>
<td>FEV1/FVC at approximately 4 months after Omalizumab therapy start</td>
<td>FEV1/FVC 1 year after Omalizumab therapy start</td>
<td>before vs. Omalizumab therapy start</td>
<td></td>
</tr>
<tr>
<td>67.1 (17.2)</td>
<td>67.6 (15.1)</td>
<td>0.8%</td>
<td>0.416</td>
<td></td>
</tr>
<tr>
<td>67.6 (10.8)</td>
<td>70.1 (9.36)</td>
<td>4%</td>
<td>0.085</td>
<td></td>
</tr>
</tbody>
</table>

A one-sided paired t-test was conducted with FEV1/FVC values before treatment start and approximately 4 months after treatment start to test if the 0.8% increase was also reflected in the mean difference of every individual’s before and after values. The test showed that there was no significant improvement after treatment (p-value of 0.416).

Finally, a one-sided paired t-test conducted with FEV1/FVC values before treatment and approximately 1 year after treatment start revealed nonsignificant changes (p-value=0.085) in values before and after treatment for each individual patient.

4.3.4 Exacerbation Frequency Before and After Treatment

The number of exacerbations experienced by patients before and after treatment was analysed (table 6). 18 patients had data for both 1 year before and for between 1-2 years after treatment start.

Table 5: Exacerbation data for before and after treatment at the chosen intervals of 1 year before treatment and between 1-2 years after Xolair® (omalizumab) treatment start (n=18). For one patient, there was no information on smoking history. Sd stands for standard deviation.

<p>| Number of Males | 7 |</p>
<table>
<thead>
<tr>
<th>Number of Females</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>55 (22-75)</td>
</tr>
<tr>
<td>Active Smokers</td>
<td>0</td>
</tr>
<tr>
<td>Previous Smokers</td>
<td>4</td>
</tr>
<tr>
<td>Mean Serum IgE Amount (sd)</td>
<td>313 IE/ml (221)</td>
</tr>
<tr>
<td>Number of Patients Currently Receiving Treatment</td>
<td>9</td>
</tr>
<tr>
<td>Mean (sd) number of exacerbations 1 year before treatment start</td>
<td>2.72 (2.74)</td>
</tr>
<tr>
<td>Mean (sd) number of exacerbations between 1-2 years after treatment start</td>
<td>3.39 (2.35)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.402</td>
</tr>
</tbody>
</table>

A two-sided paired T-test on exacerbations was preformed to test if patients had a significant change in exacerbation frequency after treatment. The test revealed no significant changes (P-value = 0.402). 14 patients had either no change or an increase in the number of exacerbation after omalizumab therapy.

An analysis of exacerbation frequency in males and females before and after treatment at the same intervals was also conducted. The results are summarised in table 7.

Table 6: Analysis of the number of exacerbations experienced by males and females before and after Xolair® (omalizumab) treatment. In total, there were 7 males and 11 females. Sd stands for standard deviation.

| Female mean (sd) exacerbation total 1 year before treatment start | 2.64 (3.47) |
| Male mean (sd) exacerbation total 1 year before treatment start | 2.86 (1.07) |
| Female mean (sd) exacerbation total between 1-2 years after treatment start | 2.81 (1.32) |
| Male mean (sd) exacerbation total between 1-2 years after treatment start | 4.29 (3.35) |

5 Discussion
Results from treatment specifications showed that most patients followed the recommended dosage table from FASS. The most common reason for terminating treatment
was because of no improvement in asthma symptoms after treatment start. The percentage of patients who experienced adverse effects was low (13%). The results showed nonsignificant improvement in FEV1 and FEV1/FVC values before and after omalizumab treatment. They also showed nonsignificant worsening of the number of asthma exacerbations experienced by patients before and after treatment.

Results from patient characteristics showed that most patients had IgE values within 30-1,500 IE/ml, the range which has dosage recommendations from FASS. Serum IgE values in patients are a determinant of dosage and interval of Xolair® (omalizumab) [12] but whether the activity or the level of IgE is the most predictive indicator that a patient will respond positively to treatment is still unclear [13]. Out of the 38 patients, none had serum IgE levels under 30 IE/ml which is the lowest level given in FASS’s dosage chart for omalizumab [12]. However, 4 patients have serum IgE values under 76 IE/ml which indicates an increased risk of the patient being a non-responder [12]. A possible explanation for this increased risk was suggested in a study that evaluated the assumption that allergen-specific IgE and serum IgE were proportionate to one another. The patient’s serum IgE and weight was used to determine omalizumab dosage, not allergen-specific IgE levels. However, it is the allergen-specific IgE that mediates the allergic asthmatic response. The study concluded that because patients with serum IgE levels between 30-75 IE/ml had a higher proportion of allergen-specific IgE in total IgE compared to patients with serum IgE levels over 75 IE/ml, they might require a higher dose of omalizumab to experience a positive response to treatment [18]. Interestingly, in this study 3 of 4 patients with serum IgE values under 76 IE/ml continued with treatment after the treatment evaluation at 16 weeks.

At the other end of the scale, 5 patients lacked a recommended dose as their serum IgE levels were too high, and only 2 of these patients continued with the therapy after the evaluation at 16 weeks. It has been suggested that patients with higher IgE may need longer evaluation periods as they are slower to respond to treatment [19], which may be an area for future study.

The most common reason for terminating treatment after the 16-week evaluation was because of no subjective or objective improvements of asthma symptoms following omalizumab treatment. The evaluation at 16 weeks is based primarily on subjective findings, such as if the patient experienced any change in allergic symptoms after treatment start. However, allergen threshold sensitivity (CD-sens) has been implemented during the last few years at the Örebro University Hospital lung clinic to objectively determine omalizumab response in patients after treatment with omalizumab for at least 16 weeks. This is of interest
because CD-sens is an objective measurement which can perhaps offer more objectivity to the clinical evaluation. CD-sens is defined by Nopp et al as “the inverted value for the allergen concentration giving a 50% maximum CD63% up-regulation multiplied by 100”, in other words, the allergen concentration required to stimulate basophil activation. This can be analysed by flow cytometry to detect basophil allergen sensitivity to allergens, with higher CD-sens values revealing higher sensitivity to an allergen. CD-sens has been shown to be an effective method of monitoring patient sensitivity to allergens during anti-IgE treatment when compared to several other methods [20]. This was because CD-sens dropped to below CD-sens values found in non-allergic patients when the omalizumab-treated allergic patients were asymptomatic [20]. It would be an interesting area of study to analyse how well CD-sens establishes omalizumab response now that CD-sens is used routinely at the lung clinic.

Cross-referencing the dosage charts from FASS with the study population’s dosage of Xolair® (omalizumab) revealed that most patients were given the recommended dosage for their weight and serum IgE levels. It should be noted for clarification that the dosage recommendations for weight and serum IgE changed 3-4 years ago. As the only difference between the dosage charts was that several of the recommendations for a two-week interval were changed to a four-week interval with a compensatory increase in injection dosage, no distinction in the results section was made for patients using the old dosage chart versus the new. For example, the previous dosage table gave the recommendation 225 mg omalizumab every 2 weeks and the new recommended prescription is 450 mg omalizumab every 4 weeks. Most patients who did not follow the recommended dosage tables had doses lower than recommended, which may have affected their response to omalizumab. A review that analysed the pharmacodynamics of omalizumab summarized that treatment response is achieved when serum IgE levels fall below 20.8 IU/ml or less. Dose, patient weight and pre-treatment IgE levels influence omalizumab’s clinical effectiveness, and these factors were taken into consideration when designing omalizumab’s dosage table [15]. Deviation from the dosage chart may result in a serum IgE level under the recommended amount for clinical benefits.

The adverse effects reported in this study were all recorded in FASS as possible adverse effects. The two most commonly reported adverse effects in this study were headaches and tiredness, which were classed by FASS as a common adverse effect (frequency ≥1/100) and a less common side-effect (frequency ≥1/1 000), respectively [12]. The most serious adverse event reported in the study was serum sickness, which affected 1 patient out of the 38. FASS reported serum sickness as having no known frequency due to lack of data. One patient was
suspected of being a second case of serum disease but this could not be confirmed by medical file data. Serum sickness is a type III hypersensitivity reaction which occurs when the immune system encounters foreign protein or serum [21]. In summary, this study’s findings were not in disagreement with pre-existing data.

Results from this study suggest that although there is an improvement in FEV1 values, this improvement is insignificant. Other studies on omalizumab’s effect on spirometry values have mixed findings. A review of 25 double-blind control studies with omalizumab reported a slight increase in FEV1 after the use of omalizumab [13]. One study showed that omalizumab reduced the acute bronchoconstriction response for allergen challenge with cat dander when compared with placebo-treated patients as shown by a 44% less reduction in FEV1 [16]. Yet not all studies showed that FEV1 values were significantly affected by treatment [14]. The nonsignificant data for the one-sided paired t-tests conducted on FEV1 and FEV1/FVC values before and after treatment (at approximately 4 months and 1 year after treatment start) were probably influenced by the small population samples. To recap, the t-test population sample concerning FEV1 included 13 patients and for the t-test concerning FEV1/FVC the sample included only 8 patients.

Surprisingly, the results from this study’s exacerbation analysis show that asthma exacerbations increased after treatment with omalizumab, although these results were insignificant. However, there were differences in data sources for before and after treatment that may have affected this outcome. Data on the number of exacerbations experienced before omalizumab was not collected systematically but was dependent on patients seeking medical attention from the lung clinic and anamnesis that directly asked patients about how many asthma exacerbations they had experienced that had required the use of per oral steroids or antibiotics. This information could not be retrieved consistently for all 38 patients. In contrast, after beginning treatment with omalizumab patients met regularly with the medical staff who administered omalizumab and asked patients if they had experienced an exacerbation since the last time they had received their omalizumab dose. This consistent data collection is likely one influencing factor as to why the number of exacerbations appears to have increased after beginning treatment with omalizumab.

In contrast with my findings, several studies suggest that omalizumab decreases asthma exacerbations. A review conducted by Normansell et al which includes 25 double-blind randomized control studies of omalizumab concluded that the number of exacerbations decreased with omalizumab use. It should be noted that there was greater uncertainty in patients with more severe forms of asthma, such as patients who required oral steroids, than in
patients more mild to moderate asthma forms. To exclude that the review had a definition of asthma exacerbations that conflicted with the definition used in this study, it should be mentioned that the authors used the definition “Asthma exacerbations as defined by "events", i.e. hospital admissions, emergency room visits, days lost from work/school, unscheduled doctor visits, increase in medication.” [13] which is not at odds with the definition used in this study.

Another review of 8 placebo-controlled studies supported the previous review, also finding an overall reduction of asthma exacerbations after omalizumab treatment [14]. These effects could not be linked to treatment duration, age or disease severity. The study’s definition of exacerbation was “defined by hospital admissions, ED visits, increase in rescue medication, or use of corticosteroids” [14] which is also similar to the one used in this study.

As for the strengths of this study, this study includes real clinical data over 11 years. As patients were required to receive their omalizumab injection at the lung clinic, there is a record that patients were receiving constant treatment at the correct interval and dosage verified by medical personnel. This gives a high adherence.

This study has several areas of limitations, some of which have already been mentioned earlier such as the discrepancy between how patients were asked about the number of asthma exacerbations they had experienced before and after treatment. Another limitation is the small sample population, which varied between 38 and 8 patients. A third is that the definition of asthma exacerbation used when reported in the medical files was not always defined. The definition of asthma exacerbation as a period of increased asthma symptoms that required the use of per oral corticosteroids or antibiotics was used when possible, but sometimes it was only reported in the medical file system that an asthma exacerbation had been experienced by a patient, and not defined further. Some confusion in interpreting asthma exacerbations was also experienced with patients who regularly consumed per oral corticosteroids for treatment of their allergic asthma, as these patients would not always have contact with the lung clinic before starting a per oral corticosteroid treatment in a period of worsening asthma symptoms.

This might have led to underreporting of asthma exacerbations before the patients started with omalizumab treatment, as after treatment start medical personnel regularly asked patients if they had experienced an asthma exacerbation since they had last been to the lung clinic. Another area of limitation is that the severity of an asthma exacerbation is not evaluated; an asthma exacerbation that required a two month hospitalization was counted the same as an asthma exacerbation that lasted a couple of days.
The last area of limitation is that there was no standardized method of analyzing the patient’s subjective experience of omalizumab in the medical file system. Medical personnel may report in the medical files that a patient’s symptoms have decreased, but because there exists no standardized survey for patient symptomology, this data could not be analyzed in the study. This presents a loss of data which could have been useful in evaluating the effects of omalizumab in real clinical practice.

An interesting area for future study would be analyzing differences between responders and non-responders to omalizumab to determine if there is a consistent predicative biomarker which can determine omalizumab response. Currently, there is no clinical biomarker which can consistently predict responder and non-responder patients [11]. One study suggested that the most reliable predictors of response to omalizumab was IL-13 in sputum supernatant and FEV1 values [19]. Another study suggested that the concentration of disease relevant IgE antibody not just the total serum IgE could be used to predict response to omalizumab [22].

6 Conclusion

In this study, the effect of Xolair® (omalizumab) in 38 patients was analysed with data extracted from the medical file system at Örebro University Hospital. Several variables were analysed, such as FEV1, FEV1/FVC values and exacerbation frequency before and after treatment, reasons for terminating treatment and adverse effects experienced by patients. The goal was to use data from real clinical practice to analyse these variables, of which statistical analysis revealed nonsignificant changes in exacerbation frequency, FEV1 values and FEV1/FVC values before and after treatment.
References


