Recherche

Omalizumab in ERS 2011, Amsterdam,

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Omalizumab in asthmatics with IgE levels > 700 IU/ml
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Introduction: Omalizumab, a monoclonal antibody against IgE, has been effectively used to control symptoms and reduce steroid requirements in asthmatics with serum IgE levels between 30-700 IU/ml and positive testing for perennial allergens. Its use when IgE levels are > 700 IU/ml is unclear.

Aim: To evaluate the response of asthmatics treated with omalizumab with IgE levels > 700 IU/ml.

Methods: A retrospective, case-controlled study was performed in an allergy referral clinic. Consecutive asthmatics treated with omalizumab ≥ 6 months with elevated IgE levels were identified, and demographic variables recorded. Systemic corticosteroid requirements, emergency room visits, hospitalizations, FEV1, Asthma Control Test (ACT) scores, medications and allergen responses were recorded for a period of 6 months pre and post treatment.

Results: Twenty-six patients with an IgE >700 IU/ml (Group 1) and 26 with an IgE of 30 to 700 IU/ml (Group 2) were identified. The mean IgE level was 2371 IU/ml (786-10979) vs. 221 IU/ml (30-578) respectively (p < 0.001). Age, gender, and weight were similar in both groups. Both, Group 1 and Group 2, had an improvement in asthma control based on the mean ACT pre and post treatment (15.6 vs. 18.9 [p=0.016] and 15.4 vs. 19 [p=0.006]) respectively. There was also a significant reduction in the frequency of systemic corticosteroid use during the 6 months pre and post treatment (2.58 vs. 0.96 and 2.62 vs. 1.23/steroid bursts) respectively (p < 0.001).

Conclusions: Omalizumab was effective in controlling asthma symptoms and reducing the need for systemic corticosteroids in patients with IgE levels > 700 IU/ml and produced clinical improvement similar to patients with IgE levels between 30-700 IU/ml.

P267
Effects of add-on omalizumab therapy on airway wall thickening in severe persistent asthma
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Background: Omalizumab has an important role in inhibiting the allergic inflammation, and it could possibly contribute to decreased airway remodeling in patients with asthma.

Aims and objectives: The aim of the study is to assess the effects of omalizumab on airway wall thickening using computed tomography (CT).

Methods: Twenty-eight patients with severe asthma were randomized to treat with conventional therapy with n = 13) or without omalizumab (n = 15) for 16 weeks. Airway dimensions were assessed by CT, and wall area corrected for body surface area (WA/BSA), percentage wall area (WA%), wall thickness (TWBSA) at the right apical segmental bronchus were measured before and after treatment. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaire (AQLQ) were also measured.

Results: Treatment with omalizumab significantly decreased WA/BSA, WA% and TWBSA (p<0.01, each) whereas conventional therapy had no change. In the omalizumab group, there were significant decrease in the sputum eosinophils (p<0.01), improved forced expiratory volume in 1s (FEV1), morning expiratory peak flow and the AQLQ score. The changes in FEV1% predicted and sputum eosinophils were significantly correlated (r=0.88, p<0.001), and r=0.72, p<0.01, respectively.

Conclusions: These findings suggest that omalizumab reduced wall thickness and airway inflammation.

P268
Decreasing dose protocol for omalizumab treatment in oral corticosteroid allergic asthma patients
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Purpose: To evaluate the viability of a protocol for the progressive decrease of omalizumab dose in allergic GINA step V asthma patients.

Methods: To enter the protocol, the patients had to be receiving treatment with omalizumab for a minimum of one year; oral corticosteroid dose had to have reached its lowest level and spirometry had to be ≥ than at entry. Intervention: a) The omalizumab dose was reduced by half; b) If patients were clinically stable after 6 months, the dose was reduced by half again; c) If needed, oral corticosteroid boosters were administered; d) When repeated boosters were needed and/or spirometry worsened, omalizumab dose was increased to the previous figure until the patient stabilized.

Results: The protocol started in July 2006 until December 2010. Forty-five adult patients (31 female) were included; three females were lost during follow-up. The omalizumab dose was decreased in 12 patients (26.6%); it was stopped in three and has not been reintroduced after 4, 12 and 21 months. These patients had been treated for 45, 34 and 18 months respectively. Of the nine remaining patients, in six
the dose was reduced and did not need to be re-increased; in three the omalizumab dose had to be increased to the initial dose at months 10, 15 and 32.

Conclusion: 1) A progressive decrease in the dose of omalizumab was feasible and safe in 26% of the patients. 2) A treatment-free window period is possible, and in one patient lasted up to 21 months.

P269
The APEX study: Retrospective review of oral corticosteroid use in omalizumab-treated severe allergic asthma patients in UK clinical practice
Neil Burnesi, on behalf of the APEX Study Investigators, Amr Radwan, Respiratory Medicine, London Chest Hospital, London, United Kingdom; Clinical Development & Medical Affairs, Novartis Pharmaceuticals UK Limited, Frimley/Camberley, Surrey, United Kingdom
Treatments that reduce oral corticosteroid (OCS) use can help reduce the burden of asthma. We retrospectively reviewed OCS-sparing in 136 omalizumab recipients (age ≥12 years) with severe persistent allergic asthma. The primary endpoint was the difference in OCS quantity given during 12 months pre- and post-omalizumab initiation. Secondary endpoints included changes in lung function, asthma exacerbations and healthcare resource utilization and OCS use in patients on continuous OCS at baseline. Mean (±SD) total quantity of OCS prescribed per year decreased by 34% (p<0.001) between the 12 months pre- (5±4.21 g) and post-omalizumab initiation (3.6±3.73 g). During 12 months post-omalizumab initiation 87 patients (64%) stopped/reduced OCS use and 66 (49%) completely stopped. Mean percent predicted FEV1 increased from 66.0±17.63% at baseline to 75.2±17.79% at Week 16 of omalizumab therapy (p=0.001). The number of asthma exacerbations decreased from 3.7±2.69 during 12 months pre-omalizumab to 1.7±1.93 during 12 months post-initiation (-53%; p<0.001). Between the 12 months preand post-omalizumab initiation there were reductions in accident/emergency visits (from 1.5±2.19 to 0.4±1.42; -70%) and hospitalizations (from 1.30±1.73 to 0.51±1.10; -61%) (both p<0.001). In 90 patients on continuous OCS at baseline, total quantity of OCS per year decreased from 6.8±4.34 g to 4.4±3.78 g (-36%; p<0.001). In conclusion: in routine UK clinical practice, omalizumab was associated with lower OCS use, improved lung function, and reduced exacerbation frequency and use of healthcare resources, versus the year pre-initiation.

P270
OPURIT: Omalizumab-protected ultra rush specific immunotherapy in severe asthmatic patients with house dust mite allergy
Thomas Harr, Peter Schmid-Grendelmeier, Allergy Unit, Dept. of Dermatology, University Hospital, Zuerich, Switzerland
Severe uncontrolled asthma is a contraindication against allergen-specific immunotherapy due to increased risks of side effects and asthma exacerbations. Omalizumab (Xolair®) has been shown to be an effective treatment for patients suffering from severe allergic asthma and to increased safety of allergen SpecificImmunoTherapy (SIT). We describe 3 patients (males, 28, 31 and 42 years) with severe asthma GINA III-IV and total serum IgE ranging from 181 to 680 IU/ml undergoing a combination of Omalizumab and house dust mite-SIT. House dust mite (HDM) allergy was confirmed by clinical history, positive skin prick tests, elevated specific serum IgE and positive conjunctival challenge tests. In all 3 patients Omalizumab was initiated according to manufacturer’s recommendation. After 3 months in all patients asthma improved requiring less inhaled drugs and an improved quality of life. The felt effect of HDM exposure was also reduced but still somehow present. Thus we added an allergen-specific immunotherapy with HDM as the asthma situation was stable now. We opted for an ultra-rush induction regimen with a total of 6 injections over 4 hours and a cumulative dose of 100,000 SQU. Patients were closely monitored. All patients tolerated the ultra-rush induction very well. The maintenance regimen of the HDM extract was then injected on a monthly base. Also Omalizumab was continued on the initial dose. Omalizumab may enable induction of allergen-specific immunotherapy with HDM in severe asthma patients otherwise not accessible to this approach. The long term effect of this combined treatment will have to be further evaluated to judge clinical and pharmacoeconomical aspects.

P271
Biological monitoring of cellular effects of omalizumab with basophil degranulation test (BAT) in severe asthma
Anna Stanziali, Francesco Perna, Diana Radicella, Carolina Vitale, Emanuela Carpentieri, Christian Russo, Matteo Sofia, Department of Lung Diseases, University Federico II Naples, Italy
The use of anti-IgE antibodies (Omalizumab) for the treatment of severe asthma is the first approach with biological drugs in this setting. IgE bound to receptor on responsive cells induce both mast cell and basophil degranulation with release of new mediators responsible of clinical features. There aren’t objective tests to demonstrate the biological effects to this treatment. We evaluated basophil degranulation during treatment with Omalizumab using a basophil degranulation test based on a one-step method of basophil staining after exposure to a specific allergen with flow cytometry that shows basophilic reactivity in vitro and their degranulation after contact with specific allergens. This method is based on recognition of peripheric blood cells positive to marking with monoclonal antibody CD123 that together with citophluorimetric caratheristic by Forward and Side Scatter and the contemporary negativity of expression of superficial antigen HLA-DR,identify basophil granocyte subset. In these cells after specific stimulation in vitro, is possible to identify IgE degranulation for the expression on the citoplasmatic surface of the antigen with monoclonal antibody CD63.
Seven patients were examined with the test baseline and after 12 and 24 months of OMA treatment. After 24 months of treatment degranulated basophil cells were 0.7% in comparison 53.9% at 12 months and 53.5% at baseline and this decrease was associated both to clinical improvements and reduction in oral corticosteroid daily dosage. Basophil degranulation test may be an appropriate method to evaluate Omalizumab biologic therapy in severe asthma where response and treatment duration are important aims.

P272
The APEX study: A retrospective review of responses of severe allergic asthma patients to omalizumab on continuous or non-continuous oral corticosteroids in UK clinical practice
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1North West Lung Centre, Wythenshawe Hospital, Manchester, United Kingdom; 2Clinical Development & Medical Affairs, Novartis Pharmaceuticals UK Limited, Frimley/Camberley, Surrey, United Kingdom
Omalizumab is an effective add-on option for patients with severe allergic asthma (who remain uncontrolled despite inhaled corticosteroid therapy), many of whom are receiving oral corticosteroids (OCS). We retrospectively reviewed records from 12 months pre- and post-omalizumab initiation in patients (age 812 years) with severe persistent allergic asthma who were or were not receiving continuous OCS. Percentages of patients reducing/stopping OCS use, changes in exacerbation rates, hospitalization and accident/emergency visit rates, overall responder rates and FEV1 all improved post-omalizumab (table). Responses were similar when comparing those who were and those who were not on continuous OCS at baseline. In conclusion, the benefits of omalizumab in patients not receiving continuous OCS at baseline were at least as great as those in patients receiving continuous OCS at baseline.

P273
Real-life effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: Pooled data from 3 UK centres
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Omalizumab is approved as add-on therapy for patients (age ≥ 6 years; European Union) with uncontrolled severe persistent allergic (IgE-mediated) asthma. Few studies have reported on omalizumab’s effectiveness on real-life outcomes in UK clinical settings. We report clinical outcomes in severe allergic asthma patients receiving omalizumab (150–600 mg q4wk or q2wk) at 3 UK centres (St Peter’s Hospital, Chertsey; Bradford Royal Infirmary; Colchester Hospital). Data were compared for 2-years pre-omalizumab and for the most recent assessment following omalizumab initiation. Patients (n=52; age 18–74 years) received omalizumab for an average of 982 days (range: 112–3839). 86.4% patients responded to treatment at 16 weeks. Following omalizumab, hospital admissions/bed days, A&E and GP visits decreased compared with pre-omalizumab (Table). Oral corticosteroid (OCS) use was also reduced post-omalizumab; mean maintenance dose of OCS pre- and postomalizumab was 12.6 and 5.7 mg/day (n=43). Overall, mean [SD] improvement in AQLQ score was +1.39 [1.80]. Asthma control also improved post-omalizumab, as shown by an overall increase in mean [SD] ACT of +7.29 [4.64]. Patients not receiving OCS at baseline (n=14) achieved higher mean [SD] AQLQ scores compared with those on OCS at baseline (n=29); 2.29 [1.23] vs 1.36 [1.77].

<table>
<thead>
<tr>
<th>Hospital admissions/bed days</th>
<th>A&amp;E and GP visits</th>
<th>OCS use over 1 year pre Omalizumab (g)</th>
<th>OCS use over 1 year post Omalizumab (g)</th>
<th>OCS reduction (%)</th>
<th>Patients reducing/stopping OCS (%)</th>
<th>RESP (n, %)</th>
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<th>n=51</th>
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<td>Post-omalizumab (n=52)</td>
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<td>50 (68.5)</td>
<td>28 (46.9)</td>
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<td>Change in exacerbations (n=51)</td>
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<td>71.78 (101.01)</td>
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<td>Change in hospitalizations (%)</td>
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<td>68.3:62.0</td>
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<tr>
<td>Change in A&amp;E visits (%)</td>
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Results from this pooled analysis demonstrate the real-life effectiveness of omalizumab in a clinical setting, further supporting the efficacy of omalizumab shown in clinical trials.

P274
ROMA (registry omalizumab in Malaga): Study of 84 patients
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P275
Long-term treatment with monoclonal antibodies anti-IgE in severe asthma: Follow-up of ten patients
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Omalizumab is a monoclonal anti-IgE antibody suggested for the treatment of very severe asthma. Duration of therapy remains an open question. We tried to evaluate the long-term response to omalizumab in a population of patients who extended the treatment beyond the 12 months period suggested by EMEA, with the aim of contributing to establish the ideal duration of the therapy. 10 patients (8 females, 2 males, mean age: 45 yrs), with severe allergic asthma, uncontrolled despite GINA Step 4 therapy, received optimized asthma therapy and omalizumab up to 36 months. They underwent complete clinical evaluation, spirometry tests and Asthma Control Test questionnaire every month.
Patients showed, after 24 months of treatment, a significant improvement of both symptoms and functional response: medium ACT score was 20, with a 19,2% improvement compared to basal value. FEV1 and MMEF showed an increase of 21% and 26%, respectively, with best values registered after 18 months. No side-effects were reported.
Long-term therapy with omalizumab in our patients was well tolerated with significant improvement of both symptoms and function, and absence of side-effects, suggesting that administration of omalizumab for longer than 12 months could be beneficial for some responders patients, despite costs.

P276
Omalizumab and voriconazole in allergic broncopulmonary aspergillosis (A case series)
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Allergic bronchopulmonary aspergillosis (ABPA) in immunocompetent patients may represent a cause of severe, difficult to control asthma associated with recurrent exacerbations and dependence to systemic steroid. We describe of 5 F patients, age mean 62.6 y (range 50 - 74) with ABPA who were treated with combined anti-IgE omalizumab and Voriconazole. They have skin prick test positive to different pollens (Parietaria, grass) and perennial allergens such as mites and Aspergillus fumigatus, but also high levels of total (732 ± 173 UI/mL) and specific IgE towards Aspergillus f. (> 25 KU/L) in the absence of invasive aspergillosis. Their treatment consisted of ICS and LABA daily and orally steroids during exacerbations (about 6-7/y).
All of the patients have CT- rhinosinusitis and Iof 5 pts has radiological signs of bronchiectasis. The PFR showed obstructive ventilatory pattern with FEV1% th = 66±6; FVC% th = 77±11 and ACT score was 17. Voriconazole 200mg bid was administrated for two months before treatment with biological therapy with Omalizumab even if the serum levels of galactomannan were negative. 3 months later treatment with voriconazole, the specific Aspergillus f. IgE levels returned normal.
After 1 year of treatment with Omalizumab, the exacerbations rate (8 vs 3) and the ACT score were reduced (21 vs 17); FEV1% th 75 improved and total IgE levels were lower (363±173 UI/mL). Second year of treatment: the specific aspergillus IgE levels returned to be high but no exacerbation was registered and ACT remained stable. In APBA patients with severe allergic asthma the combined therapy with omalizumab and voriconazole in burst might offer a longer and safer approach in this setting.

P277
Eligibility for treatment with omalizumab in Italy and Germany
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Omalizumab is an add-on therapy for patients with uncontrolled severe allergic asthma. In Europe, patients must fulfill a number of additional criteria to become eligible for omalizumab therapy, creating a challenge for epidemiology studies to
quantify the potential patient pool. Thus, and in the absence of robust data, the number of omalizumab-eligible patients has remained unclear.

To assess eligible patient numbers, the team employed an innovative chart-audit design approach to measure epidemiology variables based on patient-level data. 770 patient charts were reviewed in designated towns in Germany/Italy, in collaboration with >200 primary care physicians (PCPs) and respiratory specialists (RS). This study sample represents >50% and >70% of local RS in these designated towns of Germany and Italy, respectively. Of patient charts evaluated, 4 patients were currently receiving omalizumab. A further 31 patients (12 PCP; 19 RS) were evaluated as omalizumab-eligible (i.e. fulfilled all product label criteria) but were not receiving the drug. Extrapolating to a national level, this yields >6500 eligible patients in Germany, >3200 in Italy. Furthermore, this study sample revealed a significant number of PCPs treating uncontrolled severe asthma patients without referral to RS; these patients are not consistently evaluated for F EV, aeroallergen sensitivity as well as a qualitative understanding of severe exacerbations, and day and night-time symptoms.

This study suggests that significant numbers of omalizumab-naïve severe allergic asthma patients in Germany/Italy are eligible for omalizumab therapy; if treated, these patients may benefit from reduction in asthma exacerbations and improved asthma control and quality of life.

P278
Cytokine production profile of T-lymphocytes and frequency of regulatory T-cells in patients with allergic asthma receiving anti-IgE therapy
Ina Haasler, Johannes Weber, Iris Bellinghausen, Stephanie Korn, Joachim Saloga, Roland Buhl, Christian Taube. · Pulmonary, I. Medical Center Mainz; University Hospital, Mainz, Germany; Dept. of Dermatology, Mainz; University Hospital, Mainz, Germany
Omalizumab is a recombinant anti-IgE antibody with proven efficacy in severe allergic asthma. Little is known about immunological changes affected by decreasing free IgE during omalizumab therapy. In the present study T-lymphocyte cytokine profiles and frequency of regulatory T-cells before and during omalizumab therapy in patients with severe allergic asthma were examined.

Twenty patients with severe allergic asthma (14 female) who met the criteria for omalizumab therapy were enrolled. Before and after 16 weeks of therapy peripheral blood mononuclear cells were isolated and activated with anti-CD3/anti-CD28 antibodies. Cells were processed for intracellular cytokine staining and frequency of CD3+ CD4+ interleukin (IL) 4, 5, 10 and IFN-γ in CD3+ CD4+ T-lymphocytes (mean at baseline: IL-4 5.9±3.8%; IL-5 1.4±1.1%; IL-10 4.5±3.2%; IL-17 2.0±2.0%; IFN-γ 9.2±5.6%, intraindividual difference in week +16: IL-4 1.3±3.8% p=0.164; IL-5 0.2±1.2% p=0.474; IL-10 3.4±5.0% p=0.774; IL-17 1.4±6.4% p=0.376; IFN-γ 2.0±4.5% p=0.056).

Additionally, there was no significant change in frequency of regulatory T-cells (mean at baseline: Treg 11.4±5.7%, intraindividual difference in week +16 Treg 0.4±5.5% p=0.730).

In this study there was no significant difference of the tested intracellular cytokines before and after anti-IgE therapy. Frequency of regulatory T-cells did not change significantly 16 weeks after initiation of anti-IgE therapy.

Omalizumab inhibits IgE-induced extracellular matrix deposition by asthmatic airway smooth muscle cells
Michael Roth, Michael Tamm. Pneumology, University Hospital Basel, Basel, Switzerland
Increased serum IgE levels in allergic asthma contribute to inflammation. Neutralizing humanized anti-IgE antibodies, such as Omalizumab, effectively reduce inflammation. In this study we determined the effect of human activated IgE in the presence and absence of Omalizumab on extracellular matrix deposition by human airway smooth muscle cells (8 asthma patients; 8 healthy controls).

Confluent cells were stimulated by 5% human pooled serum or IgE (0.1 – 10 ng/ml) in the presence or absence of Omalizumab (1 – 100 ng/ml) for 72 hours in the presence of [3H]-proline (0.5 microCi) and extracellular matrix deposition was monitored. Compared to non-stimulated cells, stimulation with 5% serum increased matrix deposition by +42% and IgE dose-dependently increased matrix deposition by max. +38%. Interestingly we observed the stimulatory effect of IgE in airway smooth muscle cells of both healthy controls and asthma patients with no significant difference. When the cells were pre-incubated with Omalizumab for 30 minutes the IgE-induced matrix deposition was dose-dependently reduced. The reductive effect was 100% when ratio of Omalizumab:IgE was 10:1. Furthermore, the inhibitory effect of Omalizumab was similar when applied together with IgE or even when added 15 minutes after IgE. When added at later time points after IgE addition the inhibitory effect of Omalizumab was reduced but significant until 45 minutes. We observed no difference of either IgE induced matrix deposition or the inhibitory effect of Omalizumab comparing healthy control to asthma patient’s cells. Our results indicate that IgE increases airway remodeling and that Omalizumab significantly reduces this effect.

Anti-immunoglobulin E antibodies may improve remodeling in a mouse model of asthma
Marisa Hübner, Stephanie Korn, Matthias Jung, Ina Haasler, Christian Taube, with severe allergic asthma

Effects of omalizumab on markers of eosinophilic inflammation in patients

P3352

range postulated to be necessary for a treatment response. An adequate reduction in non-responders. These results question the free IgE target stop treatment. The relevance of free IgE measurements is limited to demonstrating omalizumab does not predict clinical response or add to the decision to continue or Monitoring free serum IgE in severe asthma patients treated with

GmbH, BecherConsult GmbH, Bernau, Germany;

Joint Research Center, Dokkyo Medical University, Koshigaya, Saitama, Japan

Recent studies have confirmed that omalizumab, an anti-immunoglobulin E (IgE) antibody, has a high response rate in patients with severe asthma who satisfy conditions such as the use of high-dose inhaled steroids and poor respiratory function. However, the effect of omalizumab on airway remodeling, a characteristic feature of chronic severe asthma, remains to be confirmed. In this study, we compared the effect of omalizumab with that of steroids in a mouse model of remodeling. BALB/c mice were continuously sensitized to ovalbumin to produce a model of remodeling. After the remodeling model had been prepared, four groups were studied: an IgE neutralizing antibody group (A), a steroid group (B), an IgE neutralizing antibody plus steroid group (C), and an untreated control group (D). Basement membrane thickening, used as a marker of remodeling, was found to be significantly inhibited in the group A, as compared with the other groups. The group B showed a trend toward inhibition of basement membrane thickening, but the effect was weaker than that in the group A. In the group C, basement membrane thickening was significantly suppressed in a synergistic fashion.

Airway remodeling, a characteristic of chronic severe asthma, was significantly inhibited by treatment with IgE neutralizing antibodies. Concurrent treatment with steroids was markedly effective. On the basis of these results, omalizumab is expected to be therapeutically effective for severe refractory asthma. The finding that treatment with steroids alone was less effective than combined treatment suggested that IgE neutralizing antibodies might also have a steroid-sparing effect.

P3350

Monitoring free serum IgE in severe asthma patients treated with omalizumab

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It is stated that benefit of omalizumab treatment in severe IgE-dependent asthma requires serum free IgE concentrations below 50 ng/ml. It is unclear if monitoring free serum IgE is clinically meaningful once omalizumab treatment is initiated. Free IgE and omalizumab serum concentrations were quantified in 22 patients with severe asthma (68% female, 47±11 yrs., mean ±SD) pre-bronchodilator FEV1 62±13%, baseline mean (±SEM) free serum IgE 652±136 ng/ml treated with omalizumab for 4 months using a Recovery-ELISA.

Omalizumab treatment reduced free serum IgE prior to the second omalizumab injection by 73%, after 16 weeks by 81% to 58±12 ng/ml (p=0.001 vs. baseline). 17 patients responded to anti-IgE therapy as judged by physician-rated global evaluation of treatment effectiveness. There was no relation between free serum IgE concentrations and treatment response. 41% of responders had free IgE levels above 50 ng/ml and 40% of non-responders below 50 ng/ml. There was no significant or clinically relevant difference regarding changes in lung function, exhaled NO, asthma control, and quality of life between patients with free IgE below or above 50 ng/ml.

Monitoring free IgE and omalizumab serum concentrations in patients treated with omalizumab does not predict clinical response or add to the decision to continue or stop treatment. The relevance of free IgE measurements is limited to demonstrating an adequate reduction in non-responders. These results question the free IgE target range postulated to be necessary for a treatment response.

P3352

Effects of omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma

Marisa Hübner, Stephanie Korn, Matthias Jung, Ina Haasler, Christian Taube, Roland Buhl. Pulmonary Department, Mainz University Hospital, Mainz, Germany

Allergic asthma is a chronic inflammatory airway disease in which immunoglobulin E (IgE) and eosinophils play important pathogenetic roles. We investigated the effect of the anti-IgE antibody omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma eligible for omalizumab treatment according to current guidelines. In 31 consecutive GINA step 4/5 patients (19 female, 48±11 yrs., 78±12 kg, 274±238 IU/ml total IgE; FEV1 at baseline 1.8±0.6 L, 61.8±19.5% pred.) omalizumab (median 450 mg/month) was administered s.c. as add-on therapy. Exhaled nitric oxide (NO), peripheral blood eosinophils and serum interleukin-5 were measured before and after 16 weeks of treatment. In all patients total daily doses of inhaled and oral corticosteroids remained stable during treatment.

23 (74%) patients responded to therapy (GETE). Baseline NO was 43±8 ppb (mean±SEM) for responders (R) and 23±6 ppb for non-responders (NR), blood eosinophils were 0.38±0.07/µl (R) and 0.25±0.06/µl (NR), and IL-5 was 7.5±1.13 (R) and 1.9±1.3 pg/ml (NR, R vs. NR p=0.030). After 16 weeks NO decreased by 3±6 ppb (R, p=0.804) and 12±18 ppb (NR, p=0.375), blood eosinophils were unchanged (R week0-week16: -0.14±0.16/µl p=0.687; NR: 0.01±0.04/µl, p=1.00), and IL-5 decreased by 3.7±1.0 pg/ml (R, p=0.012) and 0.3±1.4 pg/ml (NR, p=0.625).
In conclusion, patients with a clinical response to omalizumab had higher pretreatment serum IL-5 levels and a pronounced decrease in serum IL-5 following omalizumab. Blood eosinophils were unchanged, and exhaled NO was low prior and on treatment with omalizumab, consistent to high-dose ICS treatment.

P3948 Anti-IgE and airway remodelling: Omalizumab affects reticular basement membrane thickness in severe persistent atopic asthma
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Asthma is a complex genetic disorder that is characterized by airway inflammation and reversible airflow obstruction. Severe asthmatics are inadequately controlled despite the use of high-dose inhaled corticosteroids (ICS) and long-acting B2-agonists. Role of IgE mediated inflammation in asthma is established. Allergic inflammatory process underlies the pathogenesis of severe persistent asthma. The most widely used and currently only approved monoclonal antibody against IgE for use in asthma is Omalizumab. The efficacy and safety of omalizumab have been evaluated in several studies which showed a significant drop in asthma exacerbations, and emergency visits. The thickening of subepithelial basement membrane in severe asthma is associated to increased bronchial mucosal eosinophils, typical allergic cellular effectors. The aim of this study is to investigate the effect of anti-IgE on the basement membrane thickness. Biopsies were obtained from 11 patients with Severe Persistent Allergic Asthma. Before e post (12 months) treatment with omalizumab. RBM thickness was measured by morphometric analysis by using light microscope image analysis. The analysis proved a significantly statistical difference, p<0.005, in a narrow population. Nonetheless we explored more in detail the entire population discriminating Responder and Non Responder on the basis of the obtained reduction in RBM thickness and different cut-off. The difference between Responder and Non-Responders proved statistically significant. Present data showed that 9/11 patients reduced the original RBM after treatment with anti-IgE, thus emphasizing the role of omalizumab in affecting asthma remodelling.

P3954 Omalizumab and malignancy: Interim results from the EXCELS study
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Background: Omalizumab is a biologic for the treatment of moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids. At the time of FDA approval, the incidence of malignant neoplasms was higher among patients who had received omalizumab (0.5%) compared to placebo (0.2%) in clinical trials.
Objective: The EXCELS study is an FDA postmarketing commitment to evaluate the long-term safety of omalizumab.
Methods: EXCELS is an ongoing prospective observational study of approximately 5000 omalizumab-treated and 2500 non-omalizumab-treated moderate-to-severe persistent allergic asthma patients aged ≥12 years from 448 US centers who are followed for up to 5 years. All reported potential malignancies are reviewed by an independent oncology panel. The primary analysis includes confirmed, incident study-emergent primary malignancies.
Results: This analysis of malignancy rates was based on interim study report 6 (data through 11/30/2010) which comprises 18,860 person-years in the omalizumab cohort and 10,947 person-years in the non-omalizumab cohort. Both cohorts had an average follow-up of 3.8 person-years. The incidence of study-emergent primary malignancy was 12.78 and 14.48 per 1000 person-years in the omalizumab and the non-omalizumab cohorts, respectively, corresponding to a rate difference of -1.70 (0.2%) in clinical trials.
Conclusions: In this analysis, the incidence of malignancy was similar in the omalizumab and non-omalizumab cohorts. These interim results are preliminary and the study is still ongoing. Because the study is observational, selection and other biases cannot be excluded.
Funding Source: Genentech, Inc and Novartis Pharmaceuticals Corp.

P3959 ‘Real-life’ persistence beyond the first year of omalizumab treatment in patients with severe allergic asthma: The R-Pixel study
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Background: Omalizumab (OMA) treatment has been shown to be effective in patients with severe allergic asthma (SAA), but published data beyond the first year of treatment are scarce.
Objective: To examine the persistence rate (PR), to identify reasons for discontinuation and to determine the response rate (RR) and the clinical effectiveness beyond the first year of OMA treatment.
Methods: Of 105 patients who were on OMA treatment at the end of the 52w observational PERSIST study (RespiMed 2009: 103–1633), 53 (51%) participated in this study. A retrospective medical chart analysis was performed at approx. 16, 52,
and 68w after the end of the PERSIST study (up to 120w of treatment). Measurements included PR, physician-rated Global Evaluation of Treatment Effectiveness (GETE), Asthma-related Quality of Life Questionnaire (AQLQ), and systemic glucocorticosteroid use, emergency room (ER) visits and hospitalizations for severe exacerbations.

Results: The PR at 120w was 84.9%. Treatment was discontinued in 3 cases by patient decision (1 relocation, 1 AE, 1 non-compliance with office visits), in 3 patients by joint patient/physician decision (2 complete asthma control, 1 AE) and in 2 patients due to non-OMA related death. Where data were available, RR (good+excellent GETE) was >85%. Absolute change of ≥5 point in AQLQ score was >90% from t=0w to t=120w: less than 18.9% of patients required sGCS. There were no ER visits and only 1 hospitalization during the evaluation period.

Conclusions: These preliminary results indicate a high PR with OMA beyond the first year of treatment under "real-life" conditions in SAA patients in Belgium.

P4000
The Dutch hypothesis, implications for treatment of chronic obstructive pulmonary disease and asthma in a biomarker, monoclonal antibody world.

Experience with IgE and omalizumab in a small pulmonary practice

In 1961, Orie and colleagues from the University of Groningen in the Netherlands hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis and emphysema, should be considered not as separate entities but as different expressions of one disease entity. In a pulmonary practice patients with a physician diagnosis of chronic obstructive pulmonary disease (COPD) had physiological and biochemical evaluation as part of their routine workup. They were treated with omalizumab if they were symptomatic despite adequate conventional treatment and had an elevated IgE level. Patients with COPD (n=60) who were on treatment with omalizumab for at least 6 months were asked to fill out a questionnaire from which their symptom scores (1-4) and satisfaction scores (1-5) were extracted. There was statistically significant improvement in the amelioration of both symptoms and increase in satisfaction scores (p was less than 0.01) with treatment with omalizumab. This year being the 50th anniversary of the Dutch Hypothesis, it may be appropriate to revisit this issue. Patients with COPD may benefit from evaluation and treatment with monoclonal anti-IgE antibody therapy. Randomized placebo controlled, double blinded trials are needed to help further define the role of anti IgE therapy in patients with COPD. Subsequently, the broad use of biomarkers to evaluate need for monoclonal antibody therapy may need to be reconsidered. To the treating physician and the patient the treatment outcome is more relevant than the actual diagnosis.

P4004
No difference observed in the risk of malignancy in patients exposed to omalizumab compared with controls
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Previous pooled data from the omalizumab clinical trial programme (Phase I-III clinical studies) showed a numerical imbalance in cancers arising in omalizumab recipients. The incidence of malignancies in the omalizumab group was similar to that expected in the general population but higher compared with control, raising a question over omalizumab’s long-term safety. To fully address this potential safety concern, a further analysis was conducted using additional pooled data to examine malignancy in omalizumab-treated patients. We used data from 32 randomized, double-blind, placebo-controlled trials (RDBPCTs) to assess incidence of primary malignancy. 7432 patients (4254 omalizumab, 3178 placebo) were included. Total observation times censored at first malignancy were 3382 and 2473 patient-years whereas exposure durations of 2143.9 and 1689.1 patient-years, respectively. Malignancy rates and corresponding changes in rate ratios over time are shown in the Table.

<table>
<thead>
<tr>
<th>Year</th>
<th>Omalizumab Rate</th>
<th>Placebo Rate</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>3.56 (4 / 1124)</td>
<td>3.50 (6 / 1715)</td>
<td>1.65 (0.46, 7.31)</td>
</tr>
<tr>
<td>2006</td>
<td>3.56 (9 / 1536)</td>
<td>3.56 (11 / 2473)</td>
<td>1.20 (0.43, 3.38)</td>
</tr>
<tr>
<td>2010</td>
<td>4.45 (11 / 2473)</td>
<td>4.14 (14 / 3382)</td>
<td>0.93 (0.39, 2.27)</td>
</tr>
</tbody>
</table>

No specific cluster of morphology was identified. The primary malignancies in RDBPCT, 2003-2006 2010 Omalizumab rates* 5.86 (9 / 1536) 4.21 (9 / 2136) 4.45 (11 / 2473) Control rates* 3.56 (4 / 1124) 3.50 (6 / 1715) 4.45 (11 / 2473)

* Malignancy rates per 1000 patient-years calculated from number of malignancies/observation time.

No specific cluster of morphology was identified.

P4054
Monitoring of efficacy of therapy with monoclonal antibodies – Omalizumab – Using the Recovery-ELISA

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The Revovery-ELISA (R-ELISA) resembles a combination of a Sandwich-ELISA
for the antigen and a competitive ELISA for the therapeutic antibody. The R-ELISA is a special ELISA application for presence of an additional TAb in the measuring system. The special feature is a two-dimensional calibration, which performs a calibration for the antigen without and with addition of the therapeutic antibody and a calibration of the antigen-recovery in dependence of the therapeutic antibody.

Addition of Omalizumab to the IgE-Sandwich-ELISA reduced the optical density of the signal in a non-linear manner for the detection of IgE. At 7.2 µg/ml Omalizumab the IgE-signal is reduced for 75%. The addition of substrate to the assay enables the re-calculation for real samples. The Fig. shows the antigen recovery in dependence of Therapeutic antibody.

The therapeutic effect of the therapeutic antibody is visible on recovery curve. This curve shows the remaining percentage of free antigen = recovery under therapy. The assay runs in serum dilutions of 1:20. This recovery curve demonstrates that the efficacy of antibody therapy in concentrations higher than 2 µg/ml Omalizumab (=40 µg/ml in undiluted serum) becomes rather low. In clinical samples was found similar IgE concentration within a wide range of high Omalizumab activity.

Using the R-ELISA it will be possible to calculate a maximal effective dose of TAb.

P4826
Safety and efficacy of omalizumab in children with allergic asthma
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Background: Omalizumab (Xolair) is a humanized monoclonal antibody used in the treatment of adults and children over 12 years with severe allergic asthma. Pediatric studies are few.

Objective: A retrospective chart review of pediatric patients who received omalizumab in the past 10 years for asthma at Nationwide Children’s Hospital, Columbus, Ohio.

Results: We had 13 patients. M:F 7:6, median age 13 years (range 9-17), median duration of therapy 36 months (range 1 to 59 months), 9 African American and 4 Caucasian, duration of asthma 15 years (8 to 16). Eight are still on therapy. All patients had severe persistent asthma. Twelve patients were receiving combination therapy (ICS and LABA). Only 4 patients claimed compliance with their asthma controller therapy. Five had family history of asthma, 6 had smoking exposure. Median IgE before starting omalizumab was 249 (range 78 to 2600).
Mean BMI was 25.7 and 46% of the patients were above the 100 percentile for BMI. Comparing between one year before and during omalizumab, mean hospital admission/patient/year decreased from 1.7±2.4 to 0.58±1.4 (p<0.05). There was also a trend towards improvement in ED visits from 2.3±3.2 to 1.7±3. Mean FEV1 during one year before omalizumab therapy, at initiation of therapy and during therapy was 91±18, 94±17, and 93±11 and was not statistically different. Two of 13 patients were taken off omalizumab because of serious side effects, one with anaphylaxis and second with dilated cardiomyopathy. Anaphylaxis was noted on first dose and cardiomyopathy was diagnosed in 5th year on therapy. **Conclusion:** Omalizumab is add-on therapy for some patients with allergic asthma. Adverse reactions in children are limiting factor.