AMBITIOUS

Atopic Der**m**atitis **B**iomarker **I**dentification **T**rial **i**n **Omalizumab® Us**age

Single- arm trial to identify potential markers underlying variability in response to Omalizumab® (Xolair®) treatment in atopic dermatitis

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List of abbreviations and definition of terms

AD	Atopic dermatitis
AE	Adverse Event
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
CRF	Case Report/Record Form
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
MDS	Multidimensional scaling plot
PGA	Patient's Global Assessment
REB	Research Ethics Board
SAE	Serious Adverse Event
s.c.	subcutaneously
SCORAD	SCORing Atopic Dermatitis
SOP	Standard Operating Procedure

Study synopsis

Name of finished product: Xolair

Name of active ingredient: Omalizumab®

Title of study: Single-arm trial to identify potential markers underlying variability in response to Omalizumab® (Xolair®) treatment in atopic dermatitis

Investigators: Principal Investigator: Prof. Dr. med Stephan Weidinger; Investigators: Prof. Dr. med. Markus Ollert, Priv.-Doz. Dr. med. Kilian Eyerich, Dr. med. Michael Zirbs, Dr. med. Christian Merkel, Dr. med. Hannah Prucha

Study center(s): Department of Dermatology and Allergy, Technische Universität München, Biedersteiner Str. 29, 80802 München

Publication(s): In preparation

Study period

First patient enrolled: 07.09.2010

Last patient completed: 08.09.2012

Development phase: Phase II

Objectives:

Primary objective: To evaluate efficacy of Omalizumab® treatment in a sample of adult patients with moderate to severe AD

Secondary objectives:
1. To identify clinical and metabolomic markers that underlie variability in response to Omalizumab® treatment in AD
2. To identify metabolomic signatures associated with AD
3. To search for genetic variants correlated to AD-associated metabotypes
4. To identify Omalizumab®-specific metabolomic signatures

Methodology: Single- arm observational explorative trial; 14 applications of Omalizumab® s.c. in 14-days-intervals

Number of patients: 20 patients planned, 23 recruited, 3 drop-outs, 20 patients analyzed

Indication and main criteria for inclusion

Inclusion criteria:
- Age ≥ 18-70 years of age, body weight ≥ 20 kg and ≤ 150 kg
- Dermatological diagnosis of AD, SCORAD >=20
- A positive RAST (εCAP1) result for at least one aeroallergen specific IgE and total IgE >=100kU/l at screening (or within the previous 12 months
- Eligible to receive systemic therapy for AD in accordance to local guidelines
- Signed informed consent from patient

Exclusion criteria:

- Evidence of skin disease other than AD (e.g. psoriasis) at the inclusion time
- Treatment with systemic AD medications or any investigational drug within a 30-day washout period
- Concomitant treatment with substances interfering with the immune system.
- Permanent severe diseases, especially those affecting the immune system, except asthma
- Pregnancy or breast feeding
- History of food or drug related severe anaphylactoid or anaphylactic reaction(s)
- History or presence of epilepsy, significant neurological disorders, cerebrovascular attacks or ischemia
- History or presence of myocardial infarction or cardiac arrhythmia which requires drug therapy
- Elevated serum IgE levels for reasons other than allergy and/or urticaria (e.g.: parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich Syndrome or clinical allergic bronchopulmonary aspergillosis).
- Evidence of severe renal dysfunction or significant hepatic disease
- Evidence for active infection that in the opinion of the investigator would compromise the patient's ability to tolerate therapy.
- History of malignancy of any organ system, treated or untreated, whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
- Clinically significant laboratory abnormalities (not associated with AD) at Visit 1
- Known hypersensitivity to any ingredients, including excipients (sucrose, histidine, polysorbate 20) of the study medication or drugs related to Omalizumab® (e.g.: monoclonal antibodies, polyclonal gammaglobulin)
- Patients who are considered potentially unreliable or where it is envisaged the patient may not consistently attend scheduled study visits
- Patients with serious psychiatric and/or psychological disturbances.
- Patients with a history of drug or alcohol abuse.
- Patients who are unable to complete a patient diary or complete questionnaires on paper
- Patients with any other condition or prior/current treatment, which in the opinion of the investigator renders the patient ineligible for the study schedule.

Investigational drug: Omalizumab® 150 mg s.c. in 14 days intervals visits 1-14 with a dose escalation to 300 mg Omalizumab® s.c. in non-responders visits 8-14

Reference therapy: N.a.

Duration of treatment: 6 months

Criteria for evaluation

Efficacy: Primary: SCORAD (SCORing Atopic Dermatitis) - reduction of at least 25% from baseline. Secondary: differences in any of the analyzed quantitative metabolomic markers and IgE prior to therapy between responders and non-responders.

Safety: Number of patients with AEs (mild, moderate and severe) and SAEs

Pharmacology: None

Statistical methods: For primary outcome paired sample t-test was applied to evaluate SCORAD reduction after medication. Differences in metabolomics after medication were assessed using linear regression model adjusted for batch effects. In subgroup analysis we

estimated differences in metabolites between responder and non-responder as well as patients and controls sampled from the KORA population-based study.

Results

Efficacy: Of the 20 patients who completed the study, 4 patients responded with a very good clinical response (SCORAD reduction of more than 50%) and 4 patients showed satisfying results (SCORAD reduction between 25% and 50%), while 5 patients showed clinically no relevant changes (reduction or increase in SCORAD of less than 25%), and 7 patients experienced a deterioration of the disease (SCORAD increase).

Secondary objectives: None of the patients carrying a filaggrin (FLG) mutation (n=7) responded to therapy, while all responders (n=8) were non-FLG-mutation carriers (p=0.05), indicating that patients with a primary skin barrier deficiency are less likely to benefit from an immunomodulatory therapy with omalizumab. Baseline levels of three glycerophospholipid metabolites as well as the total sphinomyelin (SM) / total phosphatidylcholine (PC) and total SM/total SM+PC ratios examined in fasting serum showed significant differences between responders and non-responders. During therapy, metabolites of all investigated metabolic classes (glycerophospholipids, acylcarnitines, sphingomyelines, amino acids, carbohydrates) showed significant changes, i.e. changes associated with treatment, with the most pronounced differences observed for various phosphatidylcholines.

Safety: The investigator was obliged to evaluate and document all AEs and SAEs including intermittent diseases in detail in standardized CRF or SAE forms. Every SAE was to be sent within 24 hours to the Sponsor. All AEs were of mild severity, generally unrelated to study medication, and resolved with or without treatment in all patients. No deaths were reported in this study. There was three SAE, which were judged as probably unrelated to the study drug.

Aggregate summary of all SAE-events:

System organ class	Number of events
Transient ischaemic attack	1
Spinocellular carcinoma of tongue	1
Arthropathy	1

Pharmacology: Not applicable

Conclusions: The clinical improvements during the 6-months treatment period in 8 of 20 patients support other data showing good clinical response in selected patients. However, the reported number of 20 patients can only be considered as a pilot investigation without the power to draw statistical conclusions. Patients who benefit from anti-IgE treatment might be characterized by primarily immunodysregulative features rather than a skin barrier deficiency, and exhibit abnormalities of lipid metabolite profiles in serum. Mechanisms of Omalizumab® action might include modulation of levels and/or behaviour of lipids that are involved in promoting inflammation

Date of the report: 19.03.2013

Ethics and Good Clinical Practice

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC and US Code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

1 Introduction

Atopic dermatitis (AD) is the most common chronic skin disease in infants and children with prevalence rates of up to 20%. It is estimated that approximately 50% of patients with childhood atopic dermatitis show a spontaneous remission in early adolescence, but up to 50% of these patients may have recurrences in adulthood. In addition, the disease can persist into or start in adulthood, making it one of the most common skin disorders throughout all ages. In addition, the disease frequently co-occurs with other atopic disorders such as asthma and rhinitis (1). AD causes significant problems in everyday life, has been shown to lead to decreased quality of life, vitality, social functioning, and mental health, and also constitutes a high economic burden with direct and indirect cost similar of those of asthma (2).

As is the case for asthma and rhinitis, AD is often accompanied by elevated levels of total serum IgE antibodies and abberant IgE-mediated responses to otherwise harmless environmental agents (3). Therefore it has been suggested that atopic dermatitis is part of a syndrome of “atopic diseases”, in which patients may develop food allergy, AD, asthma and rhinitis in any order and in any combination over time (4). Atopy itself is defined as “personal or familial tendency to become sensitized and produce IgE antibodies in response to low doses of allergens, “usually proteins” and to “develop typical symptoms such as asthma, rhinoconjunctivitis, or AD” (5). However, the role and temporal significance of elevated IgE in atopic dermatitis is still unclear, and other recently discovered mechanisms such as epidermally produced TSLP-mediated lung inflammation may provide alternative explanations for co-association of AD and respiratory diseases (6, 7).

AD is a typical complex disease, in which many genes might act in concert with environmental factors to determine the phenotype. However, despite much effort and progress over the past 2 decades, our understanding of the complex genetic susceptibility to atopic dermatitis remains in the early stages, compared to other complex diseases. Based on reported data, so far only *FLG* appears to clearly convey a strong and consistent AD risk across all collections in all populations and in multiple large independent studies. In addition, recent genome-wide studies have also resulted in the identification of novel susceptibility genes for asthma (*ORMDL3, CHI3L1, PDE4D*) (8-10), as well as variants in the gene encoding the high affinity receptor for IgE (*FCER1A*) for total IgE (11). These genes have been replicated and functional studies have supported their relevance in asthma and atopy, whereas their potential role in AD is not clear yet.

AD shows a wide spectrum of clinical presentations, and it is unclear whether it is a single disorder with different clinical manifestations or a group of syndromes, with unique or overlapping pathophysiologic pathways that open out into a rather uniform clinical presentation. However, a rigorous definition of patient subgroups is highly desirable in order to facilitate epidemiologic, genetic and clinical investigations, and in order to develop targeted therapies. Recently, it has been suggested to define “eczema” as the disease formerly called “atopic dermatitis” or “atopic eczema”, whereas the term “atopic eczema” is reserved for those patients with AD and evidence for IgE involvement (5, 12). It is anticipated that difficulties in defining AD and its phenotypes will be overcome by identifying genetic, transcriptomic and metabolomic signatures, and that the results of molecular studies will be of great nosological significance enabling a more detailed classification of atopic disorders. A similar development already took place in other medical fields such as in

neurodegenerative diseases, many of which are now defined by their mutated genes (e.g. spinocerebellar ataxias). In the current study in line with previous studies we will use the term “atopic dermatitis” (AD) synonymously with “atopic eczema”, i.e. eczema/AD with presence of allergic sensitization.

Currently, AD treatment strategies are targeted at both the disease and its symptoms. Whereas mild cases can mostly be managed with the use of emollients and topical corticosteroids or topical calcineurin inhibitors, in cases of moderate to severe AD additional systemic treatment is needed to control the disease. Systemic immunosuppression by cyclosporine, methotrexate, or azathioprine may be used with success. These medications, however, are rather unspecific and not without side effects, and must be used with caution.

The anti-IgE monoclonal humanized antibody Omalizumab® is a biologic agent that binds to IgE at its binding site to FcεRI. Omalizumab® has been studied for safety and efficacy in over 4500 patients, and is currently indicated in patients with moderate to severe allergic asthma, 12 years and older. Up to now, more than 50.000 patients have been treated with Omalizumab® worldwide. Free IgE levels fall between 89-98% over 16 to 24 weeks of therapy. Associated with the fall in free IgE levels is a down-regulation in the expression of FcεRI receptors on Basophils and mast cells. This mechanism of action is postulated to account for the reduction of exacerbations and symptoms of allergic asthma. In the EU, Omalizumab® is licensed for severe allergic asthma, while there is an expanded indication to moderate allergic asthma in the USA (13, 14).

Although not yet formally tested, Omalizumab® could possibly have positive effects in other asthma-related IgE-mediated disorders including AD (15). So far no randomized controlled trials for the indication AD have been performed, but three published case series - the largest one examined by ourselves (16)- indicated that a subgroup of patients might benefit most from Omalizumab® treatment (17). However, the available data on Omalizumab® in AD so far does not allow the prediction of a positive response to treatment and, as noted by the authors of the studies, further studies are needed to a-priori identify those patients most likely to respond to treatment, to minimize the risk of adverse drug reactions, and to maximize the therapeutic effect.

Pharmacogenomic studies for other diseases such as rheumatoid arthritis have yielded some encouraging results, but have also shown that comprehensive and well-defined phenotypes with increasingly detailed data are needed to provide insights into the complex networks of genes, proteins, and metabolites interacting via biochemical and physical interactions to determine the phenotype and to mediate biological manipulation such as a drug intervention (18, 19). In this context, the development of analytical techniques that can simultaneously measure hundred of small molecules in a biological sample and thereby enable the extraction of useful metabolomic signatures will aid to increase our understanding of disease pathophysiology and of mechanisms responsible for drug effects (20-22).

The major advantage of metabolomic research is that metabolomics provides a snapshot view of a biological system and enables capture of information about both long- and short-term interactions of an organism and its environment, including therapy. Initial metabolomic signatures have already been associated with several complex diseases such Alzheimer's disease, cardiovascular and coronary artery disease, and type 2 diabetes (23-25). Preliminary own results on psoriasis are highly intriguing and currently subject of replication. Importantly, the number of cases needed to gain sufficient statistical power is much lower than for pure genetic association studies, in particular when combining genomic and metabolomic data. First studies in small case numbers reported significant changes of metabolic signatures secondary to treatment with repaglinide, metformin or rosiglitazone in diabetes thereby providing new insights into mechanisms of drug action (26). The power and potential of pharmacometabonomic approaches has recently also been shown in a study on acetaminophen (27). Ultimately, the combination of genomics and metabolomic data has the potential to both identify yet unknown disease pathways and provide deeper insights into drug pharmacokinetics and pharmacodynamics.

2 Study objectives

The current study aimed at evaluating the therapeutic potential of Omalizumab® in AD by intensive clinical phenotyping and targeted metabolite profiling in order to work out markers predictive of treatment response. Secondary aims included the identification of pretreatment metabotypes that are related to atopic dermatitis and genetic variants correlated to these metabotypes as well as changes in the metabolic patterns related to the mode of Omalizumab® action.

The primary objective was to identify efficacy of Omalizumab® treatment in a sample of adult patients with moderate to severe atopic dermatitis.

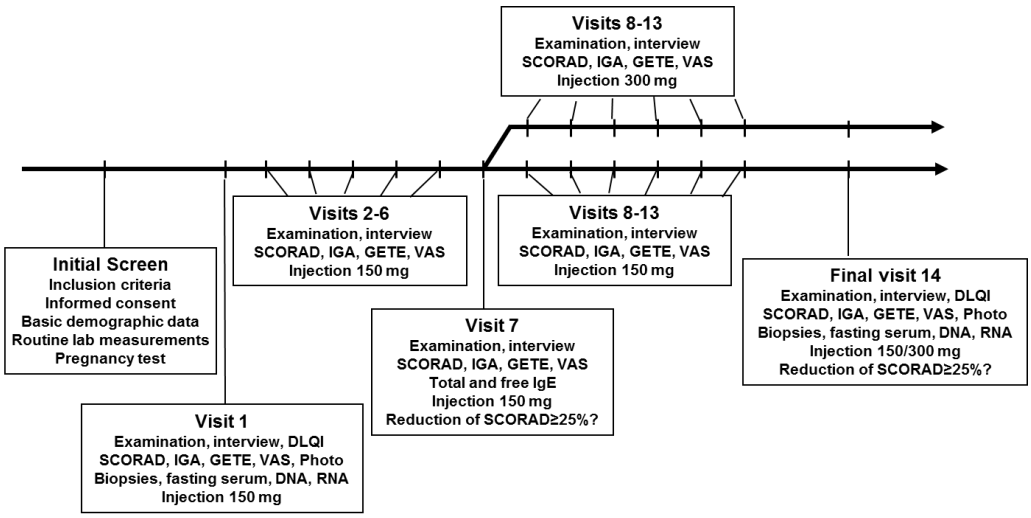
The secondary objects was to identify clinical and metabolomic markers that underly variability in response to Omalizumab® treatment in a sample of adult patients with moderate to severe atopic dermatitis, to identify metabolomic and transcriptomic signatures associated with atopic dermatitis, to search for genetic variants correlated to atopic-atopic dermatitis-associated metabotypes and to identify Omalizumab®-specific metabolomic signatures.

3 Investigational plan

3.1 Overall study design

The study was an investigator-initiated prospective monocentric, single-arm, observational 28-weeks open-label trial on a target population of 20 subjects with moderate-severe AD. A total of 23 patients were enrolled from October 2010 to September 2011. The overall study design is depicted in Fig 1.

Figure 3-1 Study design



3.2 Discussion of design

This was a single-center descriptive/exploratory-type case series to gain insights into a potential efficacy of Omalizumab® in AD, and to obtain preliminary hints for potential biomarkers predictive of therapy to be tested in future research. In the absence of a control group and a randomisation protocol, and only 20 patients finally analyzed, is must be noted that efficacy data can only be interpreted with great caution, and that the small data set may not have been sufficient to detect biomarkers.

3.3 Study population

A total of 23 adult patients suffering from moderate to severe AD with allergic sensitizations were enrolled. Of the 23 patients enrolled, 2 patients withdrew consent and 1 patient was excluded due to scheduling issues. All drop-outs occurred prior to visit 7 and were judged unrelated to the study medication. Hence, 20 patients were evaluable for analysis.

3.3.1 Inclusion and exclusion criteria

Inclusion Criteria:

- Age ≥ 18-70 years of age, body weight ≥ 20 kg and ≤ 150 kg
- Dermatological diagnosis of AD, SCORAD >=20
- A positive RAST (≥CAP1) result for at least one aeroallergen specific IgE and total IgE >=100kU/l at screening (or within the previous 12 months
- Eligible to receive systemic therapy for AD in accordance to local guidelines
- Signed informed consent from patient

Exclusion Criteria:

- Evidence of skin disease other than AD (e.g. psoriasis) at the inclusion time
- Treatment with systemic AD medications or any investigational drug within a 30-day washout period
- Concomitant treatment with substances interfering with the immune system.
- Permanent severe diseases, especially those affecting the immune system, except asthma
- Pregnancy or breast feeding
- History of food or drug related severe anaphylactoid or anaphylactic reaction(s)
- History or presence of epilepsy, significant neurological disorders, cerebrovascular attacks or ischemia
- History or presence of myocardial infarction or cardiac arrhythmia which requires drug therapy
- Elevated serum IgE levels for reasons other than allergy and/or urticaria (e.g.: parasite infections, hyperimmunoglobulin E syndrome, Wiskott - Aldrich syndrome or clinical allergic bronchopulmonary aspergillosis).
- Evidence of severe renal dysfunction or significant hepatic disease
- Evidence for active infection that in the opinion of the investigator would compromise the patient's ability to tolerate therapy.
- History of malignancy of any organ system, treated or untreated, whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
- Clinically significant laboratory abnormalities (not associated with AD) at Visit 1
- Known hypersensitivity to any ingredients, including excipients (sucrose, histidine, polysorbate 20) of the study medication or drugs related to Omalizumab® (e.g.: monoclonal antibodies, polyclonal gammaglobulin)
- Patients who are considered potentially unreliable or where it is envisaged the patient may not consistently attend scheduled study visits
- Patients with serious psychiatric and/or psychological disturbances.
- Patients with a history of drug or alcohol abuse.
- Patients who are unable to complete a patient diary or complete questionnaires on paper
- Patients with any other condition or prior/current treatment, which in the opinion of the investigator renders the patient ineligible for the study schedule.

3.3.2 Interruption or discontinuation of treatment

Predetermined reasons for withdrawal were:

- Withdrawal of informed consent
- Pregnancy
- Emergence of the following adverse events: diagnosis of cancer, severe anaphylactic or anaphylactoid reaction to study drug
- Any of the following laboratory abnormalities: Significant sustained blood dyscrasias(Neutropenia, Lymphopenia and Thrombocytopenia)
- Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.
- Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.
- Patients who are prematurely withdrawn from the study will be replaced.

3.4 Treatments

3.4.1 Investigational therapy and reference therapy

In the current study all patients, regardless of their total IgE values, were treated with a fixed schedule of 14 cycles of 150 mg Omalizumab® subcutaneously in 2-week intervals. In patients who did not reach a reduction of SCORAD ≥ 25% after 7 applications, a dose escalation was done, i.e. these patients received 300mg from visit 8 on to exclude underdosing as cause of insufficient response.
The study drug Omalizumab® was supplied by Novartis as lyophilized, sterile powder in single-use, 5 ml vials, was reconstituted with 1.4 ml sterile water and subcutaneously (s.c.) administered within 4 hours of reconstitution to the patient using a disposable 25-gauge needle and a disposable plastic tuberculin-type syringe. The injections were administered in the deltoid region on the right arm and/or left arm.

3.4.2 Treatment assignment

N.a.

3.4.3 Blinding

N.a.

3.4.4 Concomitant therapy

The concomitant use of basic emollients and topical steroids (up to class II) throughout the study was allowed.

3.4.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits were kept during the study. Drug accountability was noted by the field monitor during site visits and at the completion of the trial.

3.5 Visit schedule and assessments

Table 3.2 lists all of the assessments and indicates with an "X" the visits when they are performed. Patients should be seen for all visits on the designated day as close to it as possible. All data obtained from the assessments listed in Table 3.2 will be supported in the patient's source documentation. Patients will have visits for drug injections every 14 days (+/- 7 days). In general, the study involves: administration of study medication in 14-days intervals, standardized interviews, questionnaires, physical and dermatological exams, blood collection and collection of skin biopsies.

3.5.1 Visit schedule

Table 3 2 Visit Schedule

Visit number	**0**	**1**	**2-13**	**14**	**15**
Week	**0 Screen**	**1 Day 1**	**3-25** (+/- 7 days)	**27** (+/- 7 days)	**48 Follow -up**
Concomitant Medication	X	X	X	X	X
Informed consent	X				
Eligibility criteria	X				
Basic demographic data	X				
Medical and Allergy History (interview)	X				
Physical examination	X			X	
SCORAD/IGA	X	X	X	X	X
Dermatological examination	X****	X	X	X	X
DLQI (questionnaire)		X		X	X
Photo documentation		X	X*	X	X
Pregnancy test	X				
Central Lab Evaluation**	X			X	
AEs / SAEs		X	X	X	X***
Total and specific Serum IgE	X		X*	X	
Free IgE			X*	X	
Metabolomic profiling (fasting serum)	X		X*	X	
Expression profiling	X			X	
Skin biopsy(4mm)		X		X	
Administration of study medication		X	X	X	

* Visit 7 only; ** comprises: Hemoglobin, Hematocrit, RBC, WBC, Platelet count, Serum sodium/potassium, creatinin, uric acid total bilirubin, SGOT, SGPT, AP; *** only 2 weeks until last application of Study Medication; **** without GETE

Table 3-1 Evaluation and visit schedule

	Screening	Base-line	Day	Week			Month			End of study
Procedure / event			1	1	2	4	2	3	4	(EoS)
Informed consent	X									
Medical history	X									
Eligibility	X	X								
Vital signs		X								X
Physical examination		X								X
ECG		X				X	X	X	X	X
Blood sample for lab tests		X								X
Drug level measurements				X		X				

3.5.2 Efficacy assessments

Efficacy of Omalizumab® treatment in atopic dermatitis was evaluated by clinical disease parameters, e.g. the SCORAD (SCORing Atopic Dermatitis). A good response was defined as SCORAD-reduction of at least 25% from baseline. All investigators were experienced dermatologists who in addition were trained regarding the measurements prior to the study start by the principal investigator. Furthermore, all investigators had training sessions using an online course in scoring AD prior to the study start (http://adserver.sante.univ-nantes.fr/Scorad_Course/Course.html).

3.5.3 Safety assessments

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies, the regular monitoring of hematology, blood chemistry and urine performed at the study center or a central laboratory, and regular assessments of vital signs, physical condition and body weight. Full information about the definition of adverse events (AE) and serious adverse events (SAE), the procedure for reporting them and the assessment of other safety parameters is given in the protocol (Appendix 1.1).

3.5.4 Drug levels and pharmacokinetic assessments

None were made

4 Protocol amendments, other changes in study conduct

4.1 Protocol amendments

No protocoll amendments were submitted.

4.2 Other changes in study conduct

None occurred

5 Data management

5.1 Data collection

Designated investigator staff entered the information required by the protocol onto Case Report Forms that were printed on paper. Field monitors reviewed the Case Report Forms for completeness and accuracy, and instructed site personnel to make any required corrections or additions. The Case Report Forms were forwarded to the MSZ by the investigational site, one copy being retained at the investigational site. Once the Case Report Forms were received by the MSZ, their receipt was recorded, the original copy was placed in Central Files and the non-carbon required copy was forwarded to the responsible medical data management staff for processing. All Case Report Forms sent to the MSZ by investigational sites were reviewed upon receipt for any serious adverse events.

5.2 Database management and quality control

Data items from the Case Report Forms were entered centrally into the study database by MSZ staff using double data entry with verification upon second entry. Text items (e.g. comments) were entered once and checked manually against the Case Report Forms. Concomitant medications entered into the database were coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology. When the database was declared to be complete and accurate, the database was locked and unblinded. Any changes to the database after that time could only be made by joint written agreement between the Principal Investigator and the MSZ.

6 Statistical methods

6.1 Statistical methods

The explorative analysis was based on the “per protocol” principle” on a total of 20 patients. The primary objective was to evaluate the efficacy of Omalizumab® treatment in atopic dermatitis defined as SCORAD (SCORing Atopic Dermatitis) - reduction of at least 25% from baseline. Secondary analysis focused on exploring differences in any of the analyzed quantitative metabolomic markers (163 markers are measured) and IgE prior to therapy between responders defined as SCORAD-reduction of at least 25% from baseline and non-responders. For responder analyses, the Welch-test on log-transformed values was used. Secondary objectives comprise differences in any of the analyzed parameters prior to treatment in the study population (N=20) as compared to population controls from KORA (NK=2000). Since parameters investigated are quantitative, the Welch-test on logtransformed values is used as appropriate. For the comparison of baseline and post treatment values in IgE, TARC and metabolomic markers, methods for two dependent samples (paired t-test) are applied for the group of responders, the non-responders and both. A further secondary objective is the association of asthma or one of the morphologic variants of dermatitis with response. Comparisons of responders and non-responders with respect to asthma rates or particular variants of atopic diseases are due to the χ^2-test or Fisher’s exact test, as appropriate. Any p-values given are two-sided and not corrected for multiple testing. Due to the screening nature of the study, p-values have to be interpreted exploratively.

6.1.1 Population

Of the 23 patients enrolled, 2 patients withdrew consent and 1 patient was excluded due to scheduling issues. All drop-outs occurred prior to visit 7 and were judged unrelated to the study medication. Hence, 20 patients were evaluable for analysis.

6.1.2 Background and demographic characteristics

All study subjects were recruited at the Department of Dermatology and Allergy,University Hospital rechts der Isar, Technische Universität München. The age range was between 23 and 76 years and the male/female ratio was 9/11. All subjects received Omalizumab® every two weeks during the whole study period.

6.1.3 Concomitant therapy

The use of basic emollients and topical steroids (up to class II) was allowed throughout the study.

6.1.4 Efficacy evaluation

The primary outcome, SCORAD reduction between visit 14 and baseline (visit 1), was evaluated using the paired sample t-test. Moreover we tested whether the success rate (proportion of responder) is significantly greater than 0.5 using the binomial test. As secondary efficacy differences in metabolites between visit 14 and baseline (visit1) was assessed using linear regression model adjusted for batch effects. Model: (Visit14 - Visit1) ~ $\beta_0+\beta_1$Batch. Additionally metabolites between responder and non-responder at baseline (visit 1) were compared using median regression respectively Mann-Whitney-test on residuals derived from regression of metabolites on batches. Model: Visit1 ~ β_0 + β_1Batch + β_2Responder. Finally metabolites were compared between patients and age and sex matched control samples derived from the KORA F4 study. Model: Visit1 ~ β_0 + β_1Batch + β_2Cases/Controls. Due to significant differences in metabolomics between patients and KORA controls a z-transformation of data was used to normalize metabolomic data. Log-transformed values were used in all metabolomic analysis.

6.1.5 Safety evaluation

Safety assessments included the recording of adverse events (AEs) and serious AEs, along with evaluation of their severity, duration, and relationship to the study drug. In addition, regular monitoring of hematology and blood chemistry results, pregnancy tests, and assessment of vital signs and body weight were performed.

6.1.6 Interim analyses

Not applicable

6.1.7 Other topics

Not applicable

6.2 Sample size and power considerations

For the primary objective, the following sample size consideration holds:

Concerning efficacy, we can say that when the sample size is 20, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.219 (i.e. 21.9%) from the observed proportion for an expected proportion of 0.5 (i.e. 50%) of patients with a SCORAD reduction of at least 25% from baseline (responders). In addition, the following power considerations hold (considering SCORAD as a quantitative measurement): When the sample size is 20, a single group t-test with a 0.05 two-sided significance level will have 80% power to detect the difference between a null hypothesis mean of 0 and an alternative mean of 0.25 (i.e. a SCORAD reduction of 25% from baseline SCORAD) assuming that the standard deviation in SCORAD change from baseline to post treatment measurement is 0.37. Furthermore, with this assumed standard deviation and a group size of 20, a two-sided 95% confidence interval for a single mean will extend 0.162

(i.e. 16.2%) from the observed mean. For responder analyses of secondary objectives, the following power consideration holds: A sample size of 10 in each of two groups (responders and non-responders) will have 80% power to detect a difference in means of 0.4 (i.e. a reduction or increase of the mean of a specific metabolite level in responders compared to non-responders of 40%) assuming that the common standard deviation is 0.3 using a two group t-test with a 0.05 two-sided significance level. For the sample size calculation the issue of multiple testing was not considered due to the screening nature of this study. In addition, with this assumed standard deviation and a group size of 10, a two-sided 95% confidence interval for a single mean will extend 0.186 (i.e. 18.6%) from the observed mean.

7 Patients studied

7.1 Patient disposition

A total of 23 patients were enrolled. 2 patients withdrew consent and 1 patient was excluded due to scheduling issues. All drop-outs occurred prior to visit 7 and were judged unrelated to the study medication. Hence, 20 patients were evaluable for analysis.

7.2 Protocol deviations

There were 71 minor protocol deviations.

By definition, all patients were included in the ITT population (n = 23). Drop-outs (n = 3) were excluded from the PP population (n = 20).

7.3 Groupings for analysis

Patients were grouped as responder having SCORAD reduction of 25% at visit 7 compared to baseline level. Additional classification of responders and non-responders were applied and subsequently divided into 4 groups: non-responder (SCORAD increased), weak responder (less than 25% SCORAD reduction), good responder (SCORAD reduction between 25 and 50%) and very good responders (SCORAD reduction > 50%).

7.4 Baseline demographic and background characteristics

Table 7-1 Study population

	cases	responder	non-responder
Mean age (SD)	46 (16.36)	43.25 (17.33)	47.83 (16.18)
Sex (male/female)	9 / 11	3 / 5	6 / 6
FLG mutation carriers, n/N	**5/20**	**0/8**	**5/12**
Asthma, n/N	10/20	3/8	7/12
Mean body weight [kg] (SD)	73.15 (13.35)	76.94 (13.18)	70.63 (13.42)
Mean SCORAD score at inclusion (SD)	45.81 (15.13)	45.60 (14.88)	45.96 (16.03)
Mean OSCORAD score at inclusion (SD)	39.54 (12.33)	38.03 (11.28)	40.51 (13.40)
Geom. mean serum IgE at inclusion [IU/ml] (SD)	935.51 (4.89)	983.67 (3.99)	883.36 (6.73)
Geom. mean serum TARC at inclusion [pg/ml] (SD)	938.23 (2.29)	963.15 (2.45)	910.53 (2.26)
Mean SCORAD score at Visit 14 (SD)	40.52 (23.01)	23.13 (14.72)	53.16 (19.58)
Geom. mean serum IgE at Visit 14 [IU/ml] (SD)	88.20 (2.90)	89.25 (2.70)	87.03 (3.40)
Geom. mean serum TARC at Visit 14 [pg/ml] (SD)	687.18 (1.79)	637.90 (1.88)	748.17 (1.74)

8 Medication

8.1 Study medication

Omalizumab®

8.1.1 Dosage

For the current study all patients were treated with a fixed schedule of 14 cycles of 150 mg Omalizumab® subcutaneously in 2-week intervals. In patients who have not reached a reduction of SCORAD ≥ 25% after 7 applications, a dose escalation will be done, i.e. these patients will receive 300mg from visit 8 on.

8.1.2 Patient exposure

Treatment phase (150 mg Omalizumab® s.c. in 14 days intervals visits 1-14 with a dose escalation to 300 mg Omalizumab® s.c. in non-responders visits 8-14)

8.1.3 Drug level and pharmacokinetic data

Drug levels were not measured

8.2 Concomitant medication

Patients were allowed to use emollients and topical steroids up to class II. Other therapies that should not have been used included systemic corticosteroids, antibiotics, immunosuppressants, cytostatics, tranquilizers, hypnotic agents, tricyclic antidepressants and UV-therapy.

9 Efficacy results

9.1 Primary efficacy results

Table 9-1 Classification of patients according to response

Response	N patients
very good response (SCORAD reduction ≥ 50%)	4
good response (SCORAD reduction 25% - 50%)	4
insufficient response (SCORAD reduction < 25%)	5
no response (SCORAD increased)	7

A paired sample t-test revealed no significant differences in SCORAD after medication (p-value = 0.2437).

Table 9-2 Primary efficacy results

	n	Mean change [CI]	p-value
Binomial test	20	0.421 [0.211, 0.660]	0.6464
Paired sample t-test	20	- 0.123 [-0.337, 0.091]	0.2437

9.2 Secondary efficacy results

Table 9-3 Comparison between responder and non-responder on several parameters

	Test	p-value
Age	Welsh-Test	0.56
Gender	Fisher-Test	0.67
Filaggrin	Fisher-Test	0.05

Table 9-4 Significant differences in metabolite levels between Visit 1 and Visit 14 assessed by linear regression model adjusted for batch effects

Metabolite	P-value	Mean Visit1	Median Visit1	SD Visit1	Mean Visit14	Median Visit14	SD Visit14	absolute change	relative change (in %)
PC aa C42:2	2.15E-04	0.099	0.090	0.058	0.078	0.050	0.059	-0.04	-44.44
PC ae C30:0	3.47E-04	0.244	0.256	0.083	0.203	0.152	0.103	-0.104	-40.63
PC aa C32:3	5.29E-04	0.232	0.236	0.087	0.173	0.146	0.085	-0.09	-38.14
PC ae C38:1	8.75E-04	0.365	0.304	0.238	0.340	0.194	0.352	-0.11	-36.18
PC ae C36:2	1.82E-05	6.107	6.210	2.216	4.474	3.980	1.866	-2.23	-35.91
PC ae C36:1	8.88E-04	3.916	4.030	1.355	3.079	2.660	1.407	-1.37	-34.00
PC ae C42:1	1.11E-04	0.233	0.217	0.104	0.211	0.146	0.146	-0.071	-32.72
PC ae C34:2	8.09E-05	4.686	4.450	1.799	3.690	3.090	1.650	-1.36	-30.56
PC ae C34:3	4.61E-04	3.081	2.760	1.780	2.375	1.930	1.248	-0.83	-30.07
SFA - PC	2.36E-04	15.543	15.900	5.481	12.519	11.300	5.547	-4.6	-28.93
PC ae C34:1	7.52E-04	4.279	4.420	1.414	3.316	3.230	1.245	-1.19	-26.92
Total PC ae	2.02E-04	72.211	66.600	31.582	56.542	48.900	25.086	-17.7	-26.58
PC ae C36:3	4.34E-04	3.026	2.790	1.305	2.446	2.050	1.172	-0.74	-26.52
PC aa C34:3	4.58E-04	7.712	7.260	2.903	6.118	5.490	2.593	-1.77	-24.38
PC aa C32:0	8.47E-04	5.742	5.540	2.220	4.493	4.300	1.852	-1.24	-22.38
SM C24:0	7.57E-04	8.971	7.780	4.151	6.732	6.060	2.891	-1.72	-22.11
PC ae C36:5	4.39E-04	4.693	3.890	3.058	3.693	3.040	1.798	-0.85	-21.85
PC aa C34:2	2.57E-04	200.105	184.000	80.453	157.021	147.000	69.870	-37	-20.11
PC aa C36:2	1.25E-04	125.900	114.000	56.800	98.200	91.100	43.600	-22.9	-20.09
PC ae C44:4	2.49E-04	0.173	0.163	0.059	0.144	0.133	0.067	-0.03	-18.40
Total PC	3.88E-04	841.842	766.000	361.616	672.263	635.000	284.606	-131	-17.10
PUFA PC	3.19E-04	690.579	618.000	311.575	546.579	515.000	236.701	-103	-16.67
Trp	5.23E-04	25.116	22.900	12.522	20.225	19.100	9.800	-3.8	-16.59
H1	5.84E-04	2221.316	1876.000	1005.550	1731.316	1567.000	581.618	-309	-16.47
Total PC SM	4.37E-04	959.789	861.000	414.003	761.842	724.000	317.805	-137	-15.91
Total PC aa	4.12E-04	769.684	703.000	331.054	615.789	593.000	261.162	-110	-15.65
Essential AA	5.08E-04	407.158	382.000	197.770	361.211	328.000	151.538	-54	-14.14
Total lysoPC	8.81E-04	87.100	80.100	42.434	67.011	69.500	25.933	-10.6	-13.23
PC aa C36:3	4.92E-04	65.989	58.800	26.167	52.579	51.300	25.586	-7.5	-12.76
PC aa C38:5	9.73E-04	22.166	19.100	9.730	18.466	16.700	7.827	-2.4	-12.57
lysoPC a C14:0	2.90E-04	1.768	1.790	0.422	1.543	1.570	0.311	-0.22	-12.29
C5	1.48E-04	0.064	0.059	0.024	0.061	0.052	0.024	-0.007	-11.86
lysoPC a C18:0	8.07E-04	11.720	10.100	7.045	8.696	8.950	3.742	-1.15	-11.39
Val	1.87E-04	119.932	103.000	61.850	106.668	92.000	46.024	-11	-10.68
Ala	6.59E-04	169.221	157.000	85.306	152.547	141.000	61.566	-16	-10.19

Glucogenic AA	9.24E-04	362.368	325.000	169.063	307.421	295.000	113.060	-30	-9.23
Total AA	5.97E-04	1378.158	1284.000	625.706	1171.895	1170.000	435.240	-114	-8.88
BCAA	5.54E-04	201.263	170.000	102.654	183.995	158.000	87.498	-12	-7.06
Creatinine	4.31E-04	34.305	28.600	19.650	27.368	26.700	10.804	-1.9	-6.64
C3	9.88E-04	0.195	0.150	0.095	0.170	0.142	0.089	-0.008	-5.33
Non essential AA	8.71E-04	971.000	875.000	431.728	810.789	832.000	294.217	-43	-4.91
SM C24 1	8.70E-04	23.526	19.000	13.446	17.908	18.200	8.000	-0.8	-4.21
Pro	9.20E-04	90.589	78.900	38.710	77.468	76.100	28.151	-2.8	-3.55
Orn	6.42E-04	34.000	27.700	16.092	29.307	28.300	12.785	0.6	2.17
C0	3.22E-04	17.126	14.300	7.445	14.815	14.500	7.170	0.2	1.40

Table 9-5 Significant differences in metabolite levels between Visit 1 and Visit 7 assessed by linear regression model adjusted for batch effects

Metabolites	P-value	Mean Visit1	Median Visit1	SD Visit1	Mean Visit7	Median Visit7	SD Visit7	absolute change	relative change (in %)
PC ae C38:1	9.47E-03	0.308	0.242	0.240	0.306	0.114	0.355	-0.128	-52.89
PC ae C36:2	9.15E-03	6.703	6.210	3.428	4.896	3.150	2.998	-3.06	-49.28
PC ae C42:1	1.85E-02	0.221	0.217	0.103	0.178	0.117	0.126	-0.1	-46.08
SFA - PC	1.70E-02	15.924	15.900	6.271	12.143	9.400	5.786	-6.5	-40.88
PC ae C30:2	7.10E-03	0.086	0.059	0.055	0.075	0.035	0.068	-0.024	-40.68
PC aa C28:1	4.48E-03	1.543	1.470	0.670	1.182	0.944	0.627	-0.526	-35.78
lysoPC a C18:2	1.10E-02	13.798	11.800	7.669	9.684	7.810	5.225	-3.99	-33.81
PC aa C32:0	1.51E-02	6.055	5.540	2.642	4.378	3.670	2.036	-1.87	-33.75
H1	1.98E-02	2288.235	2050.000	1074.421	1611.059	1366.000	656.751	-684	-33.37
Total lysoPC	1.84E-02	89.329	72.900	48.115	62.006	50.200	26.647	-22.7	-31.14
PC aa C36:3	1.33E-02	68.247	58.800	30.335	50.294	40.800	24.582	-18	-30.61
Pro	2.05E-03	86.241	78.900	37.438	59.988	54.800	22.106	-24.1	-30.54
Non essential AA	1.78E-02	1003.412	853.000	478.230	695.588	609.000	223.377	-244	-28.60
Total PC	1.83E-02	885.941	766.000	403.979	647.647	551.000	279.536	-215	-28.07
Asn	1.76E-02	20.900	17.700	11.281	14.536	12.800	4.749	-4.9	-27.68
Total PC aa	1.76E-02	810.059	703.000	367.781	592.235	509.000	254.627	-194	-27.60
Val	1.85E-02	120.624	105.000	64.263	84.729	76.400	29.799	-28.6	-27.24
PC aa C36:2	1.42E-02	130.918	116.000	61.348	96.329	84.600	40.007	-31.4	-27.07
C4	1.43E-02	0.118	0.094	0.064	0.075	0.070	0.033	-0.024	-25.53
PC aa C34:2	1.13E-02	214.471	184.000	93.528	158.606	139.000	71.141	-45	-24.46
PUFA PC	1.76E-02	728.235	618.000	343.154	532.765	467.000	226.984	-151	-24.43
Glucogenic AA	1.04E-02	373.529	307.000	185.508	255.471	233.000	78.205	-74	-24.10
Ala	1.94E-03	174.188	143.000	92.895	121.318	109.000	36.872	-34	-23.78
PC aa C40:5	1.51E-02	4.723	3.940	2.223	3.369	3.180	1.611	-0.76	-19.29
PC aa C32:2	1.33E-02	1.775	1.590	0.982	1.372	1.300	1.058	-0.29	-18.24
Cit	1.59E-02	15.082	12.500	7.806	11.246	10.400	5.265	-2.1	-16.80
C0	6.47E-03	17.482	14.300	8.083	12.826	11.900	5.207	-2.4	-16.78
Creatinine	1.34E-02	34.824	28.300	21.260	24.471	23.700	9.227	-4.6	-16.25
C5	1.42E-02	0.065	0.059	0.023	0.056	0.051	0.023	-0.008	-13.56
C18:2	1.66E-02	0.037	0.025	0.029	0.024	0.022	0.010	-0.003	-12.00
Sarcosine	1.08E-02	2.948	2.390	1.702	2.075	2.130	0.730	-0.26	-10.88
Total SM / Total (SM + PC)	1.69E-02	0.124	0.121	0.022	0.124	0.124	0.017	0.003	2.48

Table 9-6 Significant differences in residual metabolite levels (after adjustment for batch effects) between responders and non-responders at visit 1 using Mann-Whitney test

Metabolite	P-value	Mean Resp.	Median Resp.	SD Resp.	Mean Non-Resp.	Median Non-Resp.	SD Non-Resp.	Absolute difference	Relative difference (in %)
PC ae C38:1	2.01E-02	0.382	0.327	0.197	0.283	0.181	0.251	-0.1455	-44.56
lysoPC a C28:0	3.38E-02	0.550	0.311	0.472	0.429	0.247	0.335	-0.0635	-20.45
C4:1	4.45E-02	0.019	0.018	0.005	0.014	0.015	0.003	-0.003	-17.14
Total SM / Total PC	4.80E-03	0.124	0.120	0.013	0.153	0.141	0.030	0.0205	17.08
Total SM / Total (SM + PC)	4.80E-03	0.110	0.108	0.010	0.133	0.124	0.022	0.016	14.88
lysoPC a C26:1	4.90E-02	2.253	2.170	0.264	2.156	2.110	0.163	-0.06	-2.76

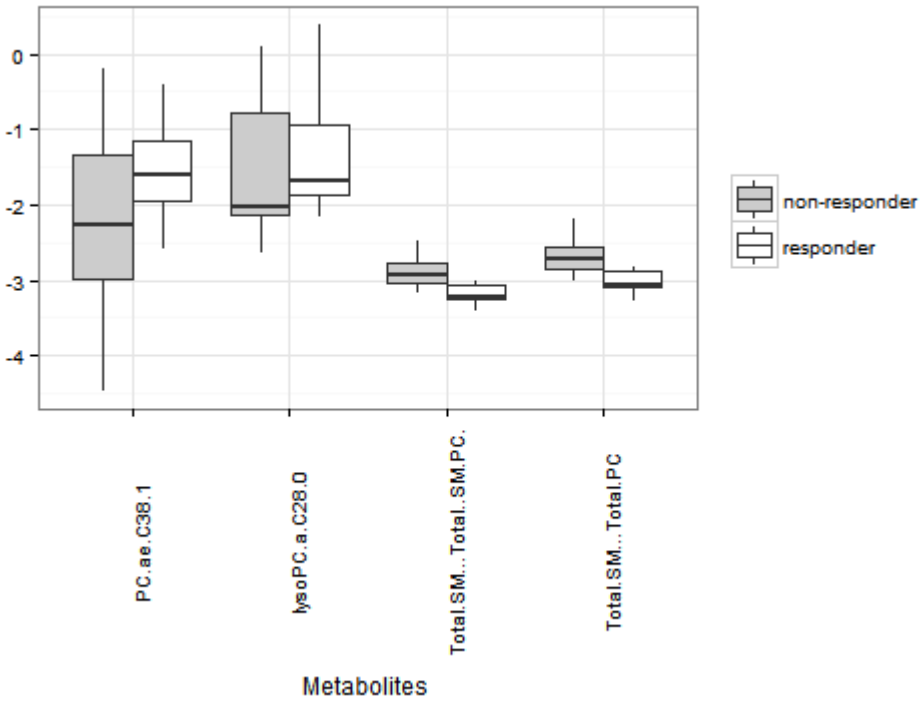


Figure 9-1 **Boxplots of the four most significantly different metabolites between responders and non-responders**

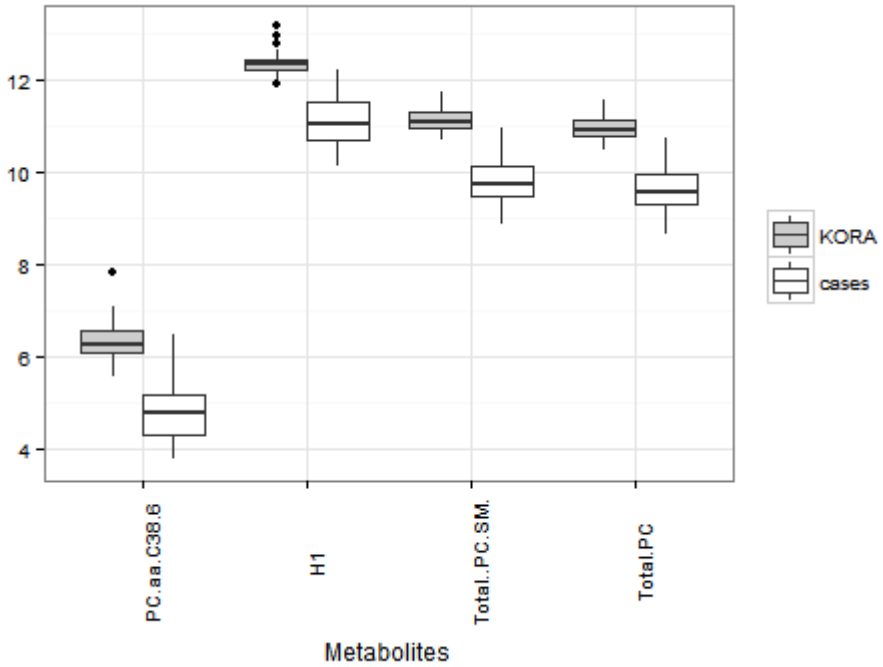


Figure 9-2 **Boxplots of the four most significantly different metabolites between cases and KORA population controls**

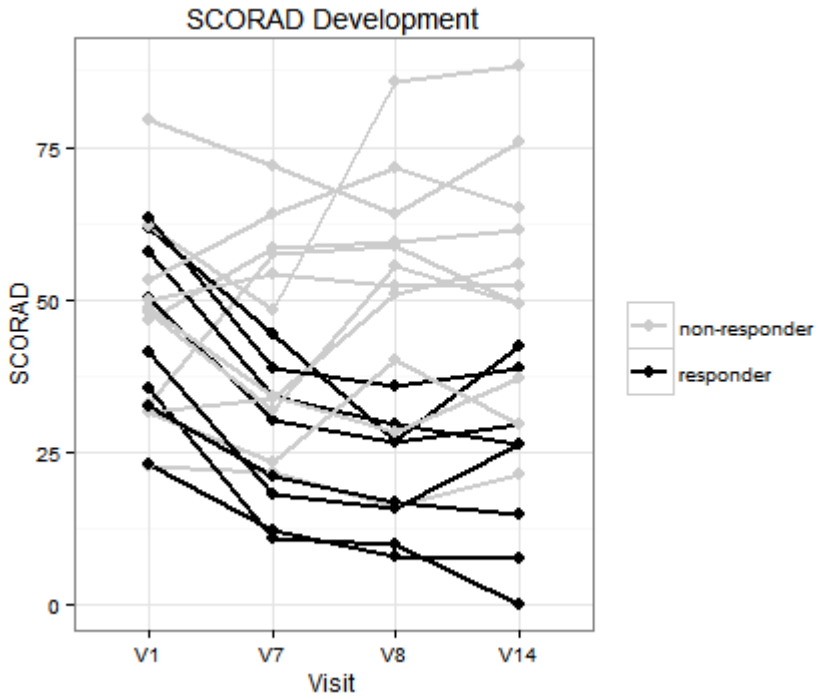


Figure 9-3 Development of SCORAD between Visit 1 and Visit 14

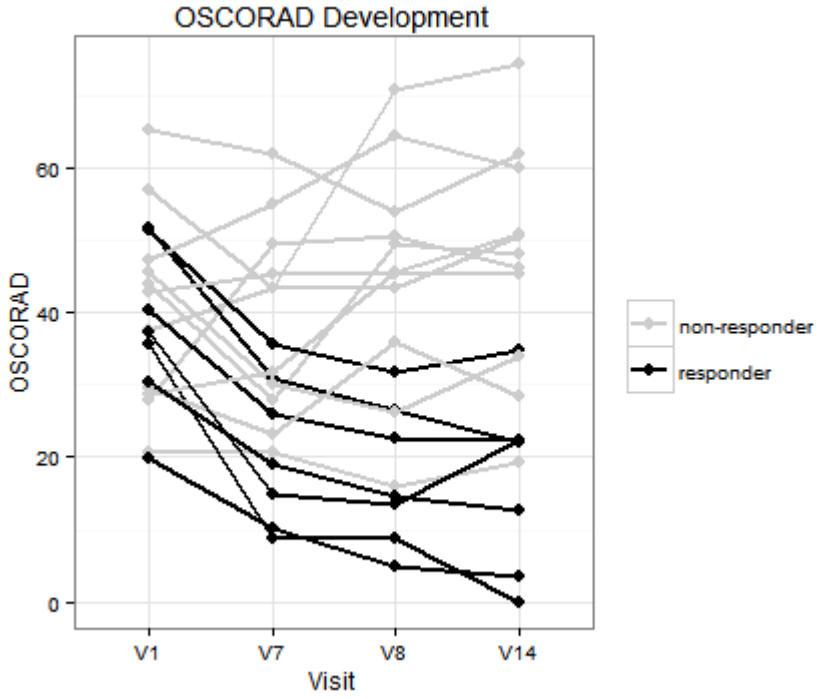


Figure 9-4 Development of objective SCORAD values between Visit 1 and Visit 14

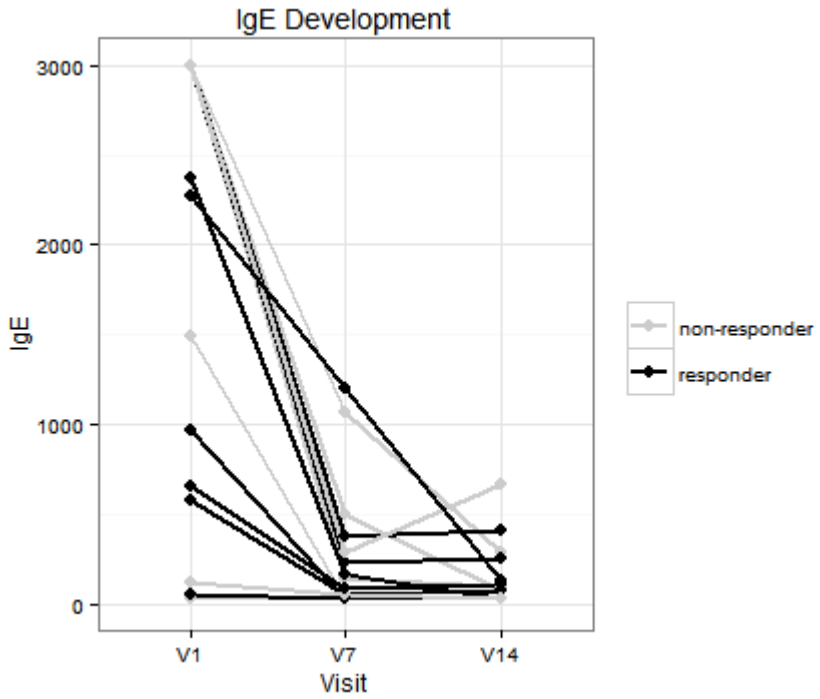


Figure 9-5 Development of IgE between Visit 1 and Visit 14

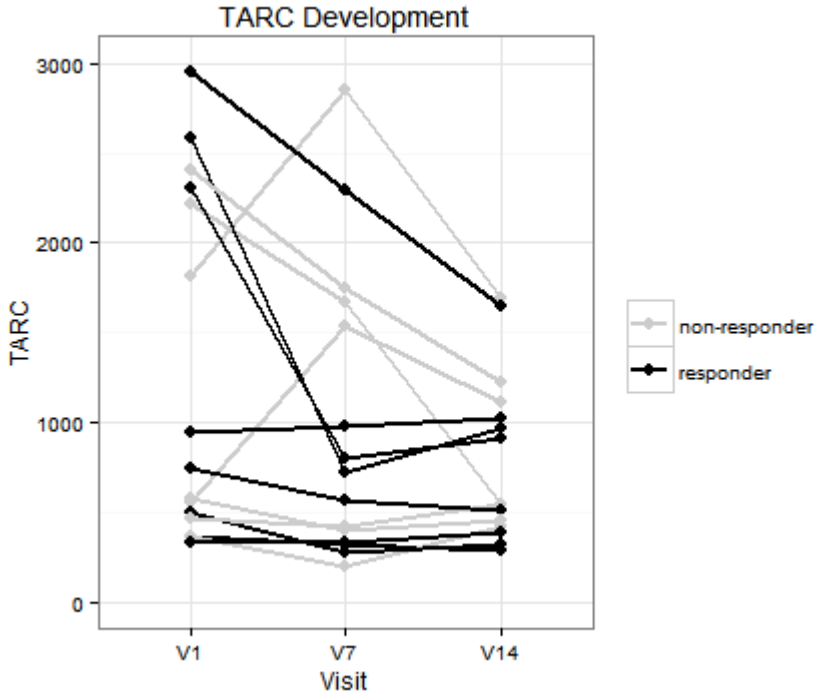


Figure 9-6 Development of TARC between Visit 1 and Visit 14

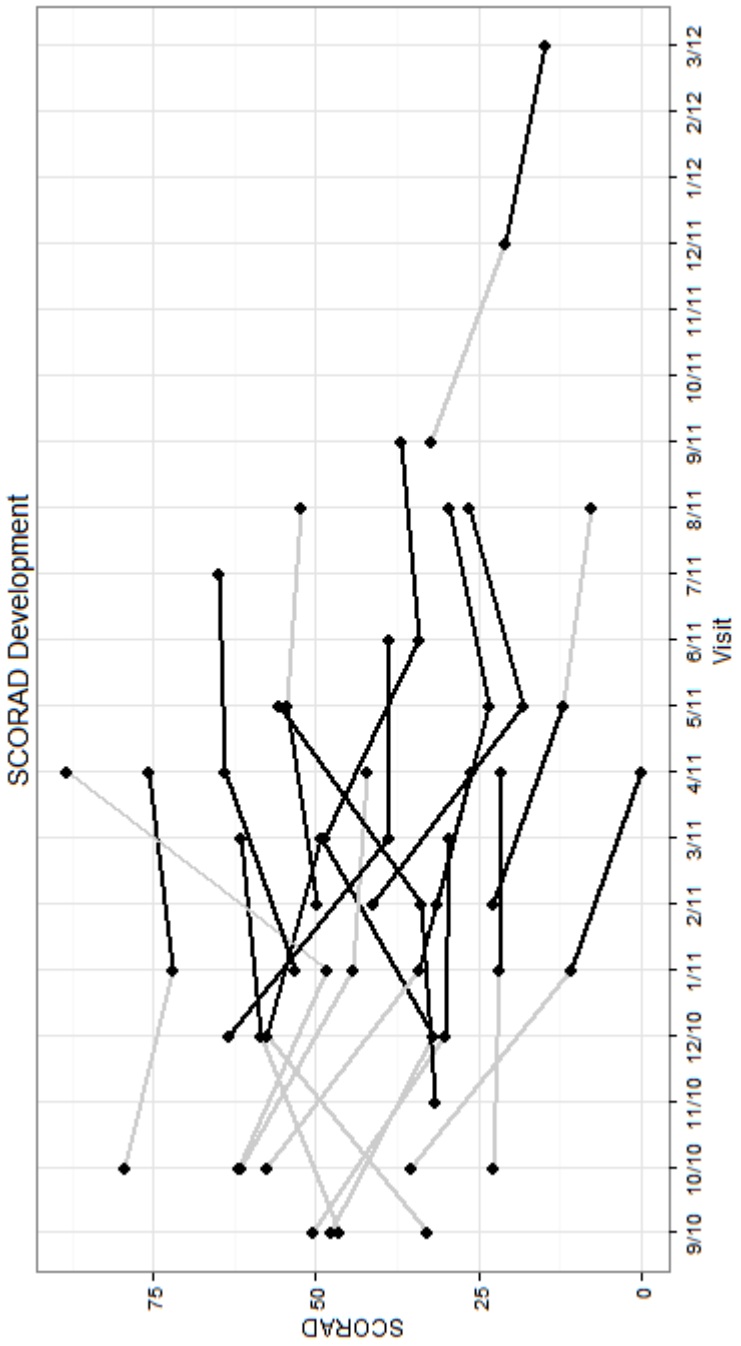


Figure 9-7 **Development of SCORAD and pollen count: black = period of allergic response. Three categories: early flowering (birch, alder, hazel) starting January 15th; grasses starting from April 15th; late flowering (mugwort) starting June 15th**

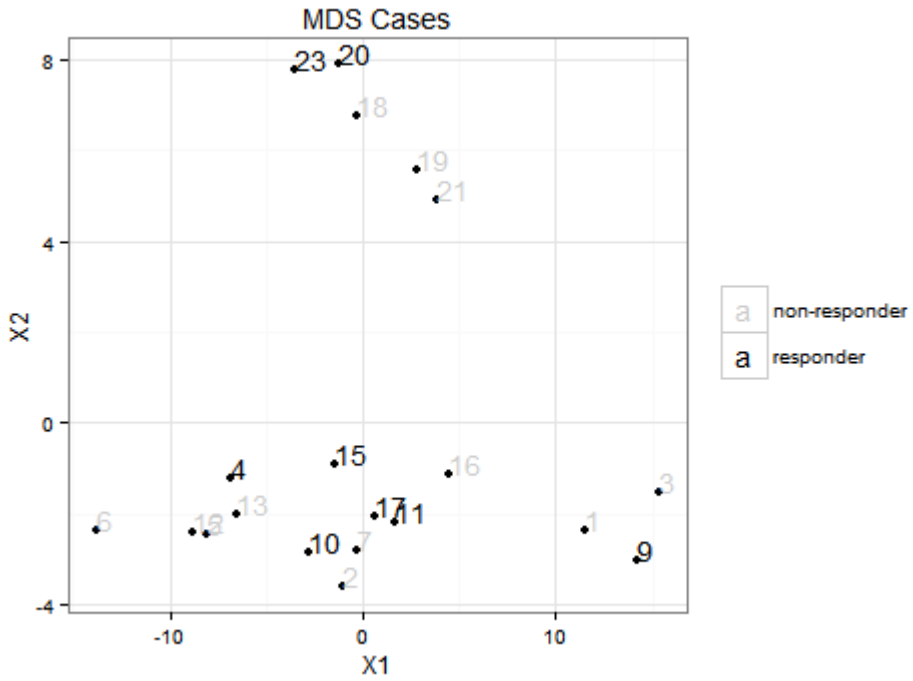


Figure 9-8 **Multidimensional scaling plot (MDS) of all measured metabolites in 20 patients. Clear separation of batch 1 (bottom) and batch 2 (top).**

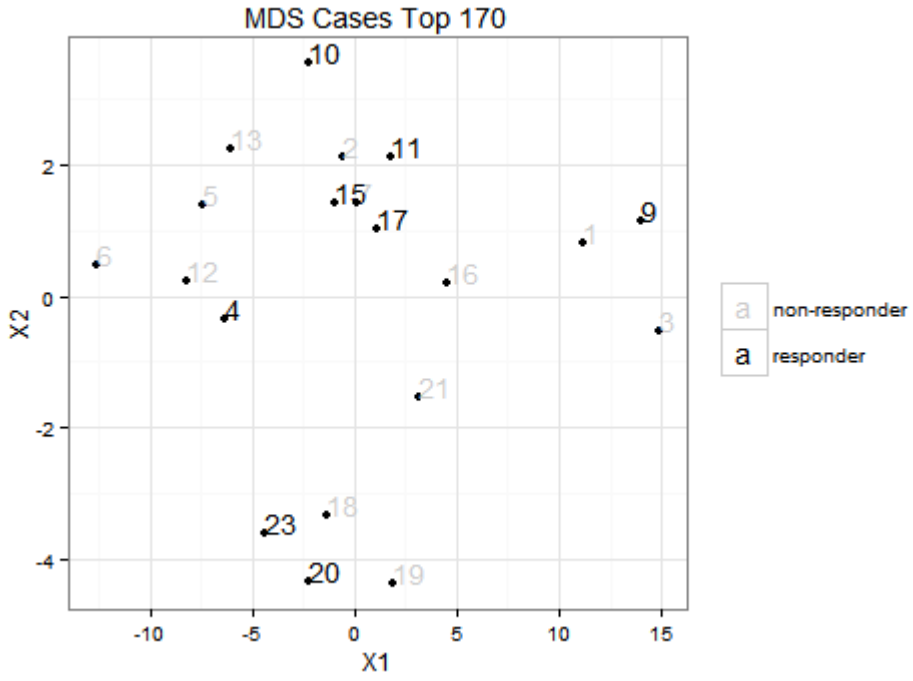


Figure 9-9 **MDS plot of the 170 most significant metabolites in all 20 patients.**

9.3 Other topics

There are no additional topics for discussion

10 Safety results

The safety information collected included adverse events (AE), results of physical examinations, data on vital signs and weight, and data from laboratory evaluations. Full details of the data collected are provided in the protocol (Appendix 1.1).

10.1 Overall experience of adverse events (AEs)

One Omalizumab®-exposed subject developed a squamous cell carcinoma (pT1 N0 M0) of the tongue. This study subject had received the last application of the study drug on April 6th 2011, and the final follow-up visit had taken place on September 26th 2011. The study subject had not informed the investigators about the AE at this follow-up visit, but the investigators were informed about it in July 2012 by the subject's resident dermatologist. According to the resident dermatologist, first signs (leukoplakia of the tongue) had been noted by him in May 2011, and an excision of the lesion had been done in January 2013. Although outside the time frame for SAE reporting, the SAE was reported to the German Novartis Clinical Safety & Epidemiology Department on July 4th 2012. According to the principal investigator's medical judgement and based on characteristics of drug action, published study data, and the Investigator's Brochure, a causal relationship between the study drug and the SAE seems unlikely, but cannot completely be ruled out. According to the resident dermatologist's information, the study subject fully recovered. An according follow-up report was sent to Novartis in January 2013. Two other SAEs (transient ischaemic attack; transient arthropathy) were considered unlikely to be related to the study medication.

10.2 Deaths, other serious and other significant adverse events

None

10.2.1 Deaths and other serious adverse events (SAEs)

None

10.2.2 Other significant adverse events

None

10.2.3 Evaluation of deaths and other serious or significant adverse events

Not applicable

10.3 Laboratory values

- Free and total IgE (visit 1, 7 and 14)
- Fasting serum concentrations of 163 metabolites, covering a biologically relevant panel of amino acids, sugars, acylcarnitines, and phospholipids (visit 1, 7 and 14)
- Genome-wide expression profiles generated from RNA derived from peripheral leukocytes and skin biopsies (visit 1 and 14)
- A venous blood sample is to be collected and sent to the central laboratory for routine examinations at screening (Visit 1), and at the end of the study (Visit 14).
- Blood samples for DNA isolation will be taken from all patients at enrolment (visit 1), and DNA extraction will be performed as described recently [33].

- Serum samples for IgE measurements will be taken from all patients at, visits 1, 7 and visit 14. IgE measurements will be carried out as described previously [34].
- Serum samples for metabolomic profiling will be taken from all patients at visit 1, 7 and visit 14. To avoid variation due to circadian rhythm, blood will be drawn in the morning between 8 and 10 am after a period of overnight fasting (12 hrs). Serum will be aliquoted and kept for 2–4 hours at 4°C, after which it will be deep frozen to −80°C until measurements.
- Targeted metabolite profiling (fasting serum concentrations of 163 endogenous metabolites, see appendix) will be carried out by electrospray ionization (ESI) tandem mass spectrometry (MS/MS) on a quantitative metabolomics platform at the Helmholtz Zentrum München.

10.4 Vital signs

No relevant changes were seen in vital signs Other safety evaluations

10.5 Special safety topics

There are no additional topics for discussion

11 Discussion and overall conclusions

11.1 Discussion

AD is a common inflammatory skin disease showing chronically relapsing eczema and high association with elevated serum IgE levels. A subgroup of AD patients requires systemic immunomodulatory treatment for long time periods. However, beyond cyclosporine A and azathioprine, only limited consent exists on systemic treatment options. Omalizumab® is a subcutaneously administered recombinant humanized monoclonal antibody, which has been firmly established as efficient therapy for allergic (IgE-mediated) asthma with a highly favourable safety and tolerability profile. IgE antibodies are also a pivotal factor in the pathophysiology of AD, and preliminary studies have indicated that at least a subgroup of AD patients might benefit from anti-IgE treatment. 59 out of 72 omalizumab-treated AD patients from published case reports and case series showed a positive clinical response (16, 28-37). However, these cases largely differ with regard to baseline characteristics and treatment regimen, and in general reports of cases and case series rank low concerning the level of evidence and at best can act as catalysts for further investigation by methods that are more systematic. In contrast, in the only randomized controlled trial on 20 patients no significant changes of clinical disease parameters were observed (38). Thus, available data so far does not allow solid conclusions on the efficacy of Omalizumab® in AD in general nor on subgroups of patients likely to benefit.

Therefore, this exploratory observational study was conducted to gain further insights into the efficacy of Omalizumab® in AD, and to analyse potential biomarkers that could help to identify the patient subgroup which benefits from Omalizumab® treatment. To this end, a target population of 20 adults with moderate-severe AD were enrolled and treated with Omalizumab®. Although the efficacy data of such a pilot clinical investigation with only 20 patients can only be interpreted with great caution, and although the placebo effects in trials with patients suffering from AD are high, our study provided suggestive evidence for an efficacy of AD at least in a subgroup of patients and at low doses, which is in line with previous reports (16). Of the 20 patients who completed the study, 4 patients responded with a very good clinical response (SCORAD reduction of more than 50%) and 4 patients showed satisfying results (SCORAD reduction between 25% and 50%), while 5 patients showed clinically no relevant changes (reduction or increase in SCORAD of less than 25%), and 7 patients experienced a deterioration of the disease (SCORAD increase). The cases showing

deterioration of their most probably experienced spontaneous flare-ups not controlled/cured by Omalizumab® rather than presenting a drug-induced negative effect. Of note, none of the patients carrying a filaggrin (*FLG*) mutation (n=7) responded to therapy, while all responders (n=8) were non-*FLG*-mutation carriers (p=0.05), indicating that patients with a primary skin barrier deficiency are less likely to benefit from an immunomodulatory therapy with omalizumab. Baseline levels of three glycerophospholipids (PC.ae.C38:1, lysoPC a C28:0, lysoPC a C26:1) as well as the total sphinomyelin (SM) / total phosphatidylcholine (PC) and total SM/total SM+PC ratios examined in fasting serum showed significant differences between responders and non-responders (table 9-6). During therapy, metabolites of all investigated metabolic classes (glycerophospholipids, acylcarnitines, sphingomyelines, amino acids, carbohydrates) showed significant changes, i.e. changes associated with treatment, with the most pronounced differences observed for various phosphatidylcholines (Tables 9-4 and 9-5). Glycerophospholipids make up approximately half of the total cellular phospholipids and comprise a substantial fraction of the lipid membranes. They contain two saturated and/or unsaturated fatty acid chains 14 to 26 carbon atoms in length with 0 to 6 double bonds. Imbalances of major lipid signalling pathways, in particular disturbances of the cellular profile of mono- and polyunsaturated fatty acids, are known to contribute to chronic inflammation, autoimmunity and allergy, and lipid signaling is of key importance in mast cells (reviewed in: (39)). Changes in SM levels can be interpreted as a result of a changed homeostasis of phosphatidylcholines, since sphingomyelin can be produced from phosphatidylcholine by the action of the sphingomyelin synthase. Interestingly, a previous population-based study showed positive associations of various polyunsaturated phosphatidylcholines (PC) levels and negative associations of several lysophosphatidylcholines (LPC) levels in fasting serum with current asthma (39), an observation which is in line with previous observations on abnormal lipid metabolism and alterations in the phospholipid compsition of serum, bronchoalveolar lavage fluid and exhaled breath in asthmatics (40-42). Further, in a pilot study on patients with rheumatoid arthritis it could be shown that lipid second messengers, in particular PC/LPC ratios in plasma represent a reliable measure of inflammation and increase upon therapy with TNF-α inhibitors (adalimumab (Humira®)) (43). Thus, our results indicate that Omalizumab® might modulate the levels and/or behaviour of lipids that are involved in promoting inflammation. Clearly, these results must to be interpreted with caution and need validation and complementation in settings with increased numbers of cases.

In line with previous reports, Omalizumab® treatment dramatically reduced serum levels of free IgE and TARC in all patients independently of their response, indicating that mechanisms other than the reduction of free IgE are responsible for the clinical response, e.g. removal of locally produced IgE and autoreactive IgE. Local IgE production has been shown in nasal mucosa of patients with symptoms of allergic rhinitis but without systemic allergic sensitization (40, 41), i.e. "local allergic rhinitis", a prevalent entity affecting 47%–62.5% of patients previously diagnosed with nonallergic rhinitis. Whether patients with AD also produce local IgE antibodies and a skin allergic response in the absence of systemic atopy is unknown. Autoreactive IgE can be found in a considerable fraction of AD patients, especially in those with severe disease (42), and are not determined in allergy testing in a routine fashion. These mechanisms are also discussed as explanation for the efficacy of omalizumab in cases of bullous pemphigoid (43), non-allergic respiratory disease forms (44), and chronic spontaneous urticaria. However, further research has to confirm the existence and to identify the relevance of local or autoreactive IgE in AD.

11.2 Conclusions

In conclusion, data from this small-scale pilot study indicate that there is a beneficial effect of anti-IgE treatment on a particular subgroup of patients with AD, and that large-scale metabolic profiling can potentially assist the classification and prediction of treatment response and investigation of mechanisms of action. Patients who benefit from anti-IgE

treatment are possibly characterized by immunodysregulative features rather than a primary skin barrier deficiency, and exhibit abnormalities of lipid metabolite profiles in serum. More extended and randomized controlled studies are needed to validate these assumptions.

12 Reference list

1. Bieber T. Atopic dermatitis. N Engl J Med. 2008 Apr 3;358(14):1483-94.

2. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Jr., Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatr Dermatol. 2005 May-Jun;22(3):192-9.

3. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. J Allergy Clin Immunol. 2003 Aug;112(2):252-62.

4. Wuthrich B, Schmid-Grendelmeier P. The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ("extrinsic") and the nonallergic ("intrinsic") AEDS. J Investig Allergol Clin Immunol. 2003;13(1):1-5.

5. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004 May;113(5):832-6.

6. He R, Oyoshi MK, Garibyan L, Kumar L, Ziegler SF, Geha RS. TSLP acts on infiltrating effector T cells to drive allergic skin inflammation. Proc Natl Acad Sci U S A. 2008 Aug 19;105(33):11875-80.

7. Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. PLoS Biol. 2009 May 19;7(5):e1000067.

8. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007 Jul 26;448(7152):470-3.

9. Ober C, Tan Z, Sun Y, Possick JD, Pan L, Nicolae R, et al. Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. N Engl J Med. 2008 Apr 17;358(16):1682-91.

10. Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, et al. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. American journal of human genetics. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2009 May;84(5):581-93.

11. Weidinger S, Gieger C, Rodriguez E, Baurecht Hr, Mempel M, Klopp N, et al. Genome-Wide Scan on Total Serum IgE Levels Identifies FCER1A as Novel Susceptibility Locus. PLoS Genetics. 2008;4(8):e1000166.

12. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001 Sep;56(9):813-24.

13. Chiang DT, Clark J, Casale TB. Omalizumab in asthma: approval and postapproval experience. Clin Rev Allergy Immunol. 2005 Aug;29(1):3-16.

14. Hamelmann E, Wahn U. Anti-IgE therapy. Clin Allergy Immunol. 2008;21:415-27.

15. Casale TB, Stokes J. Anti-IgE therapy: clinical utility beyond asthma. J Allergy Clin Immunol. 2009 Apr;123(4):770-1 e1.

16. Belloni B, Ziai M, Lim A, Lemercier B, Sbornik M, Weidinger S, et al. Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. J Allergy Clin Immunol. 2007 Nov;120(5):1223-5.

17. Andres C, Belloni B, Mempel M, Ring J. Omalizumab for patients with severe and therapy-refractory atopic eczema? Curr Allergy Asthma Rep. 2008 May;8(3):179-80.

18. Ranganathan P. Pharmacogenetics of therapies in rheumatoid arthritis. Drugs Today (Barc). 2005 Dec;41(12):799-814.

19. Koster ES, Rodin AS, Raaijmakers JA, Maitland-van der Zee AH. Systems biology in pharmacogenomic research: the way to personalized prescribing? Pharmacogenomics. 2009 Jun;10(6):971-81.

20. Kaddurah-Daouk R, Kristal BS, Weinshilboum RM. Metabolomics: a global biochemical approach to drug response and disease. Annu Rev Pharmacol Toxicol. 2008;48:653-83.

21. Schnackenberg LK. Global metabolic profiling and its role in systems biology to advance personalized medicine in the 21st century. Expert Rev Mol Diagn. 2007 May;7(3):247-59.

22. Illig T, Gieger C, Zhai G, Romisch-Margl W, Wang-Sattler R, Prehn C, et al. A genome-wide perspective of genetic variation in human metabolism. Nat Genet. 2009 Dec 27.

23. Bain JR, Stevens RD, Wenner BR, Ilkayeva O, Muoio DM, Newgard CB. Metabolomics applied to diabetes research: moving from information to knowledge. Diabetes. 2009 Nov;58(11):2429-43.

24. Greenberg N, Grassano A, Thambisetty M, Lovestone S, Legido-Quigley C. A proposed metabolic strategy for monitoring disease progression in Alzheimer's disease. Electrophoresis. 2009 Apr;30(7):1235-9.

25. Shah SH, Hauser ER, Bain JR, Muehlbauer MJ, Haynes C, Stevens RD, et al. High heritability of metabolomic profiles in families burdened with premature cardiovascular disease. Mol Syst Biol. 2009;5:258.

26. Bao Y, Zhao T, Wang X, Qiu Y, Su M, Jia W. Metabonomic variations in the drug-treated type 2 diabetes mellitus patients and healthy volunteers. J Proteome Res. 2009 Apr;8(4):1623-30.

27. Clayton TA, Baker D, Lindon JC, Everett JR, Nicholson JK. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. Proc Natl Acad Sci U S A. 2009 Aug 25;106(34):14728-33.

28. Kim DH, Park KY, Kim BJ, Kim MN, Mun SK. Anti-immunoglobulin E in the treatment of refractory atopic dermatitis. Clin Exp Dermatol. 2012 Oct 22.

29. Sheinkopf LE, Rafi AW, Do LT, Katz RM, Klaustermeyer WB. Efficacy of omalizumab in the treatment of atopic dermatitis: a pilot study. Allergy Asthma Proc. 2008 Sep-Oct;29(5):530-7.

30. Thaiwat S, Sangasapaviliya A. Omalizumab treatment in severe adult atopic dermatitis. Asian Pac J Allergy Immunol. [Case Reports]. 2011 Dec;29(4):357-60.

31. Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ. Treatment of recalcitrant atopic dermatitis with omalizumab. J Am Acad Dermatol. 2006 Jan;54(1):68-72.

32. Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. Journal of the American Academy of Dermatology. 2005 Aug;53(2):338-40.

33. Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I. Efficacy of anti-IgE therapy in patients with atopic dermatitis. J Am Acad Dermatol. 2006 Jul;55(1):168-70.

34. Quist SR, Ambach A, Goppner D, Quist J, Franke I, Bonnekoh B, et al. Long-term Treatment of Severe Recalcitrant Atopic Dermatitis with Omalizumab, an Anti-immuno-globulin E. Acta Derm Venereol. 2012 Oct 5.

35. Ramirez del Pozo ME, Contreras Contreras E, Lopez Tiro J, Gomez Vera J. Omalizumab (an anti-IgE antibody) in the treatment of severe atopic eczema. J Investig Allergol Clin Immunol. 2011;21(5):416-7.

36. Park SY, Choi MR, Na JI, Youn SW, Park KC, Huh CH. Recalcitrant atopic dermatitis treated with omalizumab. Ann Dermatol. 2010 Aug;22(3):349-52.

37. Caruso C, Gaeta F, Valluzzi RL, Romano A. Omalizumab efficacy in a girl with atopic eczema. Allergy. [Case Reports]. 2010 Feb;65(2):278-9.

38. Heil PM, Maurer D, Klein B, Hultsch T, Stingl G. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges. [Randomized Controlled Trial]. 2010 Dec;8(12):990-8.

39. Ried JS, Baurecht H, Stuckler F, Krumsiek J, Gieger C, Heinrich J, et al. Integrative genetic and metabolite profiling analysis suggests altered phosphatidylcholine metabolism in asthma. Allergy. 2013 Mar 1.

40. Rondon C, Romero JJ, Lopez S, Antunez C, Martin-Casanez E, Torres MJ, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. The Journal of allergy and clinical immunology. 2007 Apr;119(4):899-905.

41. Rondon C, Dona I, Lopez S, Campo P, Romero JJ, Torres MJ, et al. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. Allergy. [Research Support, Non-U.S. Gov't]. 2008 Oct;63(10):1352-8.

42. Tang TS, Bieber T, Williams HC. Does "autoreactivity" play a role in atopic dermatitis? The Journal of allergy and clinical immunology. 2012 May;129(5):1209-15 e2.

43. Messingham KN, Srikantha R, DeGueme AM, Fairley JA. FcR-independent effects of IgE and IgG autoantibodies in bullous pemphigoid. J Immunol. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, Non-P.H.S.]. 2011 Jul 1;187(1):553-60.

44. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. The Journal of allergy and clinical immunology. [Clinical Trial

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2013 Jan;131(1):110-6 e1.