

BRIEF COMMUNICATION

Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines

M. Hotze¹, H. Baurecht^{1,2}, E. Rodríguez¹, N. Chapman-Rothe³, M. Ollert⁴, R. Fölster-Holst¹, J. Adamski^{5,6}, T. Illig⁷, J. Ring⁴ & S. Weidinger¹

¹Department of Dermatology, Allergology and Venerology, University Hospital Schleswig-Holstein, Kiel; ²Graduate School of Information Science in Health (GSISH), Technische Universität München, Munich; ³Novartis Pharma GmbH, Nuremberg; ⁴Department of Dermatology and Allergy Biederstein, Technische Universität München, Munich; ⁵Institute of Experimental Genetics, Genome Analysis Center, Helmholtz Zentrum München, Neuherberg; ⁶Chair of Experimental Genetics, Technische Universität München, Munich; ⁷Hannover Unified Biobank, Hannover Medical School, Hannover, Germany

To cite this article: Hotze M, Baurecht H, Rodríguez E, Chapman-Rothe N, Ollert M, Fölster-Holst R, Adamski J, Illig T, Ring J, Weidinger S. Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines. *Allergy* 2013; DOI: 10.1111/all.12234.

Keywords

anti-IgE; atopic dermatitis; filaggrin; metabolomics; omalizumab.

Correspondence

Prof. Dr. Stephan Weidinger, Department of Dermatology, Venereology and Allergy, University Hospital Schleswig-Holstein, Campus Kiel, Schittenhelmstrasse 7, 24105 Kiel, Germany.
Tel.: +0049-431-597-2732
Fax: +0049-431-597-1815
E-mail: sweidinger@dermatology.uni-kiel.de

Abstract

Omalizumab, a monoclonal antibody targeting IgE, is an established therapy for severe allergic asthma and has shown efficacy in chronic spontaneous urticaria. Small-scale studies indicated some beneficial effect also in atopic dermatitis (AD). To evaluate the efficacy of omalizumab in AD and to identify markers associated with treatment response, we conducted a prospective 28-week open-label trial on 20 adults with moderate-to-severe AD. Our results confirm previous observations of a positive response in a subgroup of patients and suggest that responders are characterized by the absence of filaggrin mutations and altered lipid metabolite profiles with high levels of various glycerophospholipids.

Accepted for publication 5 July 2013

DOI:10.1111/all.12234

Edited by: Hans-Uwe Simon

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disorders. Atopic dermatitis frequently co-occurs with other atopic disorders such as asthma and rhinitis, and many patients (especially those with moderate or severe disease in secondary care settings) exhibit increased total IgE levels and sensitizations to food and environmental allergens. However, the role and temporal significance of IgE in AD are, at present, unresolved (1).

Current AD treatment strategies are mostly unspecific anti-inflammatory or immunosuppressive. However, given the high degree of heterogeneity of AD in terms of disease mechanisms, triggers and clinical presentation, stratification of patients and targeted treatment approaches are needed (2, 3).

Omalizumab (Novartis, Basel, Switzerland) is a recombinant humanized monoclonal antibody which is subcutaneously administered. It is approved for severe allergic (IgE-mediated)

asthma with an excellent safety and tolerability profile (4). More recently, it has been shown that it is also highly efficacious in chronic spontaneous urticaria (5). Omalizumab has also been investigated in various other conditions (6–8). For AD, a number of case series and one randomized placebo-controlled trial (RCT) delivered conflicting results, indicating that only a subgroup of patients benefit from omalizumab treatment. However, available data so far do not allow the prediction of a positive treatment response (9).

To gain further insights into the efficacy of omalizumab in moderate-severe AD, a target population of 20 adults (age range 23–76 years, nine men) were enrolled. The aim was to analyse potential biomarkers that could help to identify the patient subgroup that benefits from omalizumab treatment within an investigator-initiated prospective single-arm observational 28-week open-label trial (ClinicalTrials.gov Identifier: NCT01111111).

tifier: NCT01179529). Study design, inclusion and exclusion criteria, and patient characteristics are shown in Fig. S1 and Tables S1 and S2. In brief, all patients, regardless of their total IgE values, were treated with a fixed schedule of 14 cycles of 150 mg omalizumab in 2-week intervals. Patients who did not achieve a reduction in SCORAD (SCORing Atopic Dermatitis) $\geq 25\%$ after seven applications received 300 mg from visit 8 onwards. The concomitant use of emollients and topical steroids (up to class II) throughout the study was allowed.

Although placebo effects in trials with patients suffering from AD are high and data of a pilot clinical investigation with only 20 patients can only be interpreted with great caution, our study provides suggestive evidence for an efficacy of omalizumab at least in a subgroup of patients. Of the 20 patients who completed the study, four patients showed a very good clinical response (SCORAD reduction $\geq 50\%$) and four patients responded with satisfying results (SCORAD reduction 25–50%), while five patients showed no relevant clinical changes (reduction or increase in SCORAD $< 25\%$), and seven patients experienced a deterioration of the disease (SCORAD increase). The latter most probably experienced spontaneous flare-ups not controlled by omalizumab rather than presenting a drug-induced negative effect.

Of note, none of the seven patients carrying a filaggrin (*FLG*) mutation responded to therapy, while all eight responders were non-*FLG*-mutation carriers ($P = 0.05$, Fisher's test), indicating that patients with a primary skin barrier deficiency are less likely to benefit from an immunomodulatory therapy with anti-IgE.

Targeted metabolite quantification in fasting serum (10) obtained at baseline and visit 14 showed significantly higher baseline levels of three glycerophospholipids (PC:ae.C38:1, lysoPC a C28:0 and lysoPC a C26:1) as well as lower total sphingomyelin (SM)/total phosphatidylcholine (PC) and total SM/total SM + PC ratios in responders when compared with nonresponders (Table 1). During therapy, metabolites of all investigated metabolic classes (glycerophospholipids, acylcar-nitines, sphingomyelins, amino acids, carbohydrates) showed significant decreases, that is changes associated with treatment, with the most pronounced differences again observed for various polyunsaturated PCs (Table 2).

Imbalances in major lipid signalling pathways, in particular disturbance of the cellular profile of mono- and polyunsaturated fatty acids, are known to contribute to chronic inflammation, autoimmunity and allergy (reviewed in ref. 11). Interestingly, a previous population-based study showed positive associations

of various polyunsaturated PC levels in fasting serum with current asthma (10). This is in line with previous observations on abnormal lipid metabolism and alterations in the phospholipid composition of serum, bronchoalveolar lavage fluid and exhaled breath in asthmatics (12–14). Further, in a pilot study on patients with rheumatoid arthritis, it has been shown that lipid second messengers, in particular PC/LPC ratios in plasma, represent a measure of inflammation and increase upon therapy with TNF- α inhibitors (15). Thus, our results indicate that omalizumab might modulate the levels and/or behaviour of lipids that are involved in promoting inflammation. Clearly, our results are preliminary, must be interpreted with caution and need validation in settings with increased numbers of cases.

In line with previous reports, omalizumab treatment dramatically reduced serum levels of free IgE and the Th2 cell-attracting thymus and activation-regulated chemokine (TARC) in all patients, independent of their response (Figs S2 and S3). Thymus and activation-regulated chemokine has been shown to be a marker of skin inflammation and AD severity, which correlates with IgE levels (16, 17). Our findings thus suggest that in only a subpopulation of patients with AD, the simple reduction in free IgE with associated anti-inflammatory effects (18) is enough to achieve a clinical response.

In conclusion, data from this pilot study indicate that a particular subgroup of patients with AD can benefit from anti-IgE treatment. These patients are possibly characterized by the absence of *FLG* mutations and thus immunodysregulative features rather than a primary skin barrier deficiency and might exhibit specific lipid metabolism profiles characterized by increased PC species in fasting serum. Our data suggest that metabolic profiling can potentially assist the classification of patients and the prediction of treatment response as well as the investigation of mechanisms of action. More extended and controlled studies are needed to validate these assumptions. If they can be confirmed, then deeper and more extensive analyses that address the mechanism of metabolomics changes are warranted.

Acknowledgments

This work was supported by a grant of Novartis Pharma, Nürnberg (Germany), given to Stephan Weidinger. Stephan Weidinger acted as consultant to Novartis. Nadine Chapman-Rothe is employed by Novartis.

We thank Beate Schossow from the Münchner Studienzentrum (MSZ).

Table 1 Most pronounced differences in residual metabolite levels between responders and non-responders

Metabolite	P-value	Mean responders	Median responders	SD responders	Mean non-responders	Median non-responders	SD non-responders	Absolute difference	Relative difference (%)
PC ae C38:1	2.01E-02	0.382	0.327	0.197	0.283	0.181	0.251	−0.145	−44.56
lysoPC a C28:0	3.38E-02	0.550	0.311	0.472	0.429	0.247	0.335	−0.063	−20.45
Total SM/Total PC	4.80E-03	0.124	0.120	0.013	0.153	0.141	0.030	0.020	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

Table 2 Significant differences in metabolite levels between visit 1 and visit 14

Metabolite	P-value	Mean visit 1	Median visit 1	SD visit 1	Mean visit 14	Median visit 14	SD visit 14	Absolute change	Relative change (%)
PC aa C42:2	2.15E-04	0.099	0.090	0.058	0.078	0.050	0.059	-0.040	-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	-0.090	-38.14
PC ae C38:1	8.75E-04	0.365	0.304	0.238	0.340	0.194	0.352	-0.110	-36.18
PC ae C36:2	1.82E-05	6.107	6.210	2.216	4.474	3.980	1.866	-2.230	-35.91
PC ae C36:1	8.88E-04	3.916	4.030	1.355	3.079	2.660	1.407	-1.370	-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	-1.360	-30.56
PC ae C34:3	4.61E-04	3.081	2.760	1.780	2.375	1.930	1.248	-0.830	-30.07
SFA - PC	2.36E-04	15.543	15.900	5.481	12.519	11.300	5.547	-4.600	-28.93
PC ae C34:1	7.52E-04	4.279	4.420	1.414	3.316	3.230	1.245	-1.190	-26.92
Total PC ae	2.02E-04	72.211	66.600	31.582	56.542	48.900	25.086	-17.700	-26.58
PC ae C36:3	4.34E-04	3.026	2.790	1.305	2.446	2.050	1.172	-0.740	-26.52
PC aa C34:3	4.58E-04	7.712	7.260	2.903	6.118	5.490	2.593	-1.770	-24.38
PC aa C32:0	8.47E-04	5.742	5.540	2.220	4.493	4.300	1.852	-1.240	-22.38
SM C24:0	7.57E-04	8.971	7.780	4.151	6.732	6.060	2.891	-1.720	-22.11
PC ae C36:5	4.39E-04	4.693	3.890	3.058	3.693	3.040	1.798	-0.850	-21.85
PC aa C34:2	2.57E-04	200.105	184.000	80.453	157.021	147.000	69.870	-37.000	-20.11
PC aa C36:2	1.25E-04	125.900	114.000	56.800	98.200	91.100	43.600	-22.900	-20.09
PC ae C44:4	2.49E-04	0.173	0.163	0.059	0.144	0.133	0.067	-0.030	-18.40
Total PC	3.88E-04	841.842	766.000	361.616	672.263	635.000	284.606	-131.000	-17.10
PUFA PC	3.19E-04	690.579	618.000	311.575	546.579	515.000	236.701	-103.000	-16.67
Trp	5.23E-04	25.116	22.900	12.522	20.225	19.100	9.800	-3.800	-16.59
H1	5.84E-04	2221.316	1876.000	1005.550	1731.316	1567.000	581.618	-309.000	-16.47
Total PC SM	4.37E-04	959.789	861.000	414.003	761.842	724.000	317.805	-137.000	-15.91
Total PC aa	4.12E-04	769.684	703.000	331.054	615.789	593.000	261.162	-110.000	-15.65
Essential AA	5.08E-04	407.158	382.000	197.770	361.211	328.000	151.538	-54.000	-14.14
Total lysoPC	8.81E-04	87.100	80.100	42.434	67.011	69.500	25.933	-10.600	-13.23
PC aa C36:3	4.92E-04	65.989	58.800	26.167	52.579	51.300	25.586	-7.500	-12.76
PC aa C38:5	9.73E-04	22.166	19.100	9.730	18.466	16.700	7.827	-2.400	-12.57
lysoPC a C14:0	2.90E-04	1.768	1.790	0.422	1.543	1.570	0.311	-0.220	-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	-1.150	-11.39
Val	1.87E-04	119.932	103.000	61.850	106.668	92.000	46.024	-11.000	-10.68
Ala	6.59E-04	169.221	157.000	85.306	152.547	141.000	61.566	-16.000	-10.19
Glucogenic AA	9.24E-04	362.368	325.000	169.063	307.421	295.000	113.060	-30.000	-9.23
Total AA	5.97E-04	1378.158	1284.000	625.706	1171.895	1170.000	435.240	-114.000	-8.88
BCAA	5.54E-04	201.263	170.000	102.654	183.995	158.000	87.498	-12.000	-7.06
Creatinine	4.31E-04	34.305	28.600	19.650	27.368	26.700	10.804	-1.900	-6.64
C3	9.88E-04	0.195	0.150	0.095	0.170	0.142	0.089	-0.008	-5.33
Nonessential AA	8.71E-04	971.000	875.000	431.728	810.789	832.000	294.217	-43.000	-4.91
SM C24 1	8.70E-04	23.526	19.000	13.446	17.908	18.200	8.000	-0.800	-4.21
Pro	9.20E-04	90.589	78.900	38.710	77.468	76.100	28.151	-2.800	-3.55

Author contributions

MH and HB performed data analysis, interpretation and writing of the manuscript. ER, JA and TI performed biosampling and metabolite measurements. MO contributed to designing the study collection of phenotype information and performed laboratory measurements. NC, RF and JR contributed to interpretation of results. SW designed and supervised the study, planned experiments and contributed to interpretation of data and writing of the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

N. Chapman-Rothe is an employee of Novartis. S. Weidinger reports financial support for this IIT from Novartis Pharma GmbH, as well as research support from Pfizer and Biogen. J. Ring has received research support from the organizations ALK Abelló, Allergopharma, Almirall-Hermal, Astellas, Bencard, Biogen-Idec Research, Galderma, Glaxo SmithKline, Leo, MSD, Novartis, Phadia, PLS Design and Stallergenes. J. Adamski is a consultant to Biocrates AG. The other authors of the paper declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Criteria for inclusion and exclusion.

Table S2. Study population.

Figure S1. Study design.

Figure S2. Development of IgE between Visit 1 and Visit 14.

Figure S3. Development of TARC between Visit 1 and Visit 14.

References

- Garmhausen D, Hagemann T, Bieber T, Dimitriou I, Fimmers R, Diepgen T et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy* 2013;**68**:498–506.
- Novak N, Simon D. Atopic dermatitis – from new pathophysiologic insights to individualized therapy. *Allergy* 2011;**66**:830–839.
- Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy* 2012;**67**:1475–1482.
- Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N et al. Persistence of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy* 2011;**66**:671–678.
- Groffik A, Mitzel-Kaoukhov H, Magerl M, Maurer M, Staubach P. Omalizumab – an effective and safe treatment of therapy-resistant chronic spontaneous urticaria. *Allergy* 2011;**66**:303–305.
- Lavaud F, Bonniaud P, Dalphin JC, Leroyer C, Muller D, Tannous R et al. Usefulness of omalizumab in ten patients with severe occupational asthma. *Allergy* 2013;**68**:813–815.
- Tillie-Leblond I, Germaud P, Leroyer C, Tétu L, Girard F, Devouassoux G et al. Allergic bronchopulmonary aspergillosis and omalizumab. *Allergy* 2011;**66**:1254–1256.
- Kopp MV. Role of immunomodulators in allergen-specific immunotherapy. *Allergy* 2011;**66**:792–797.
- Babu KS, Polosa R, Morjaria JB. Anti-IgE – emerging opportunities for Omalizumab. *Expert Opin Biol Ther* 2013;**13**:765–777.
- Ried JS, Baurecht H, Stückler F, Krumsiek J, Gieger C, Heinrich J et al. Integrative genetic and metabolite profiling analysis suggests altered phosphatidylcholine metabolism in asthma. *Allergy* 2013;**68**:629–636.
- Wymann MP, Schneider R. Lipid signalling in disease. *Nat Rev Mol Cell Biol* 2008;**9**:162–176.
- Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med* 2011;**183**:441–448.
- Almstrand AC, Josefson M, Bredberg A, Lausmaa J, Sjövall P, Larsson P et al. TOF-SIMS analysis of exhaled particles from patients with asthma and healthy controls. *Eur Respir J* 2012;**39**:59–66.
- Lundström SL, Yang J, Källberg HJ, Thunberg S, Gafvelin G, Haeggström JZ et al. Allergic asthmatics show divergent lipid mediator profiles from healthy controls both at baseline and following birch pollen provocation. *PLoS ONE* 2012;**7**:e33780.
- Fuchs B, Schiller J, Wagner U, Häntzschel H, Arnold K. The phosphatidylcholine/lysophosphatidylcholine ratio in human plasma is an indicator of the severity of rheumatoid arthritis: investigations by 31P NMR and MALDI-TOF MS. *Clin Biochem* 2005;**38**:925–933.
- Jahnz-Rozyk K, Targowski T, Paluchowska E, Owczarek W, Kucharczyk A. Serum thymus and activation-regulated chemokine, macrophage-derived chemokine and eotaxin as markers of severity of atopic dermatitis. *Allergy* 2005;**60**:685–688.
- Morita E, Takahashi H, Niihara H, Dekio I, Sumikawa Y, Murakami Y et al. Stratum corneum TARC level is a new indicator of lesional skin inflammation in atopic dermatitis. *Allergy* 2010;**65**:1166–1172.
- Rabe KF, Calhoun WJ, Smith N, Jimenez P. Can anti-IgE therapy prevent airway remodeling in allergic asthma? *Allergy* 2011;**66**:1142–1151.

Supplement

Table S1 Criteria for inclusion and exclusion

Inclusion criteria:

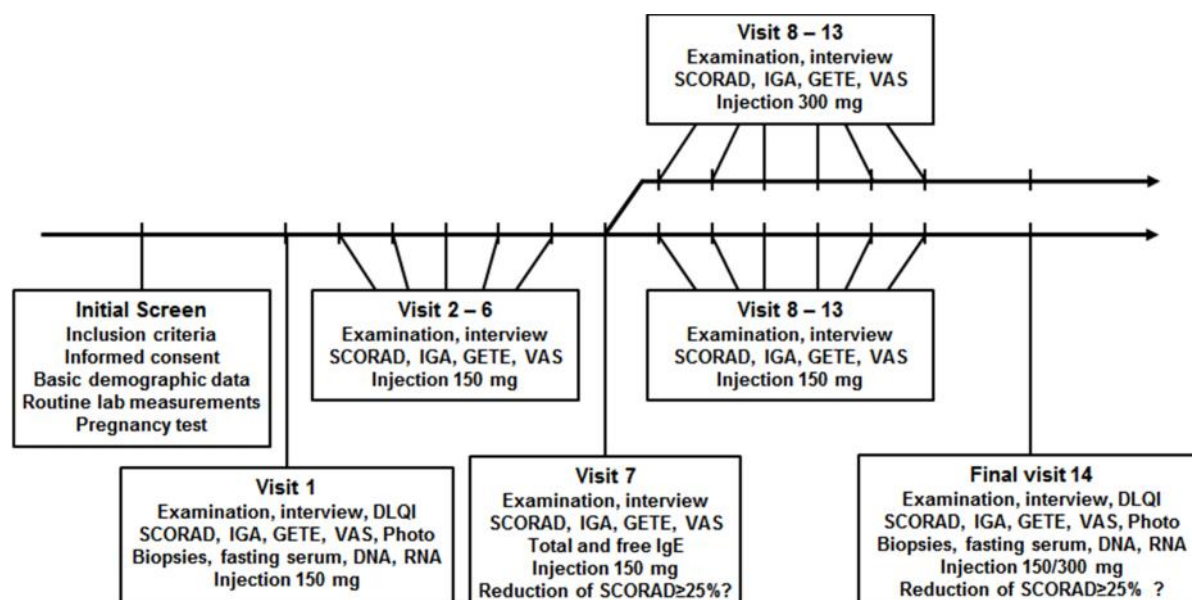
- Age $\geq$ 18-70 years of age, body weight $\geq$ 20 kg and $\leq$ 150 kg
- Dermatological diagnosis of AD, SCORAD $\geq$ 20
- A positive RAST (ϵ CAP1) result for at least one aeroallergen specific IgE and total IgE $\geq$ 100kU/l at screening (or within the previous 12 months)
- Eligible to receive 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.

Table S2 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)

**Figure S1 Study design**

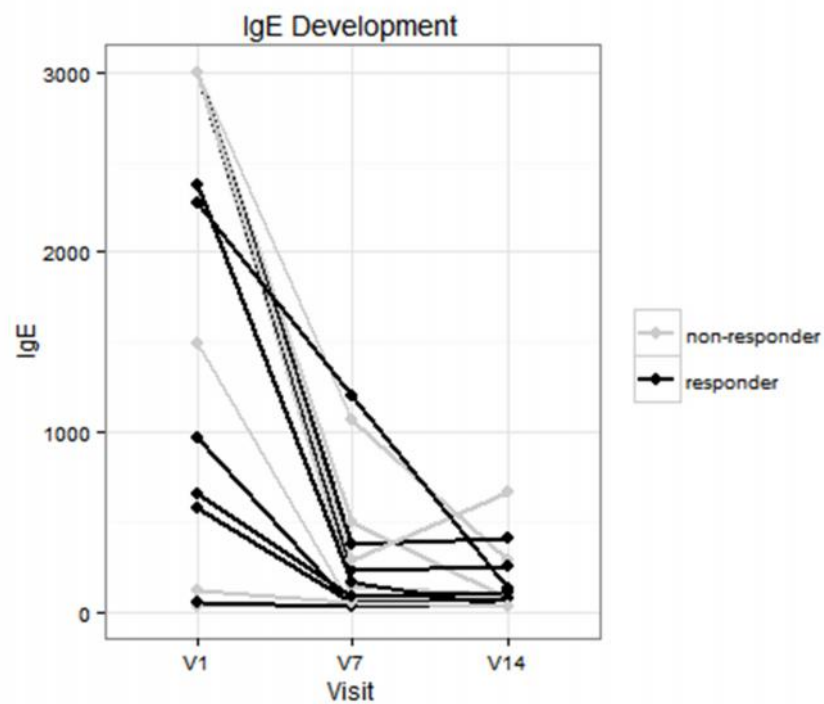


Figure S2 Development of IgE between Visit 1 and Visit 14

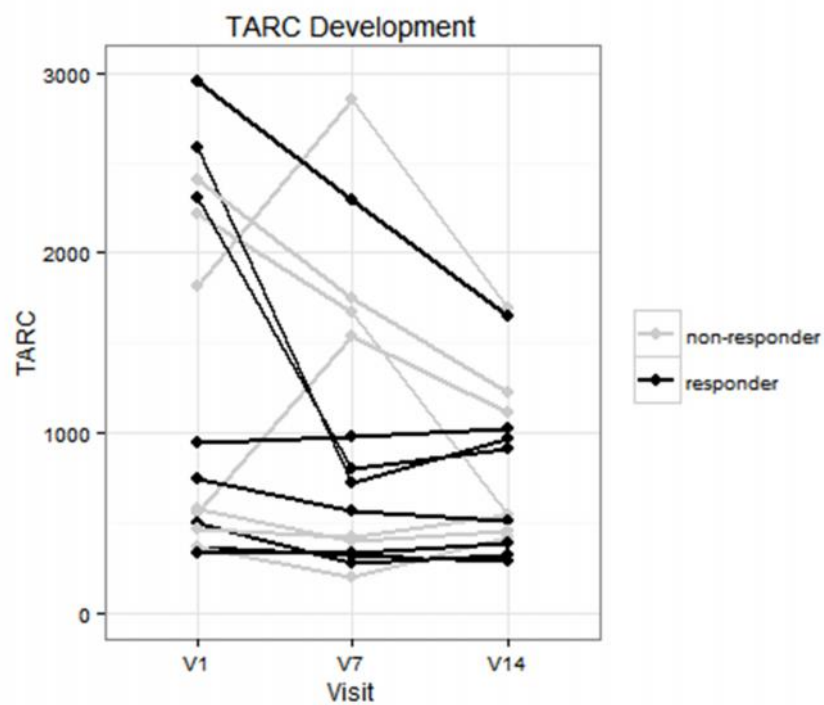


Figure S3 Development of TARC between Visit 1 and Visit 14