

in 17 of 24 (71%) children. These results open the field to new drug associations with targeted therapies or immunotherapies (Haworth et al., 2017; Reilly et al., 2017).

CONFLICT OF INTEREST

SB received research grants from Pierre Fabre Laboratory and Fondation pour la dermatite atopique, personal fees from Bioderma, Laboratoire La Roche Posay, Sanofi-Genzyme, AbbVie; non-financial support from AbbVie, Novartis, Janssen. OZ received personal fees from Novartis and was investigator for Novartis. PW received fees from Pierre Fabre and was an investigator for Novartis. ES, SF, PB, SB-G, and LV-A state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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REFERENCES

- Bhola P, Banerjee S, Mukherjee J, Balasubramaniam A, Arun V, Karim Z, et al. Pre-clinical in vivo evaluation of rapamycin in human malignant peripheral nerve sheath explant xenograft. *Int J Cancer* 2010;126:563–71.
- Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in

neurofibromatosis type 1-related plexiform neurofibromas. *N Engl J Med* 2016;375:2550–60.

Haworth KB, Arnold MA, Pierson CR, Choi K, Yeager ND, Ratner N, et al. Immune profiling of NF1-associated tumors reveals histologic subtype distinctions and heterogeneity: implications for immunotherapy. *Oncotarget* 2017;8:82037–48.

Hua C, Zehou O, Ducassou S, Minard-Colin V, Hamel-Teillac D, Wolkenstein P, et al. Sirolimus improves pain in NF1 patients with severe plexiform neurofibromas. *Pediatrics* 2014;133:e1792–7.

Johannessen CM, Johnson BW, Williams SMG, Chan AW, Reczek EE, Lynch RC, et al. TORC1 is essential for NF1-associated malignancies. *Curr Biol* 2008;18:56–62.

Reilly KM, Kim A, Blakely J, Ferner RE, Gutmann DH, Legius E, et al. Neurofibromatosis type 1-associated MPNST state of the science: outlining a research agenda for the future. *J Natl Cancer Inst* 2017;109(8).

Robertson KA, Nalepa G, Yang F-C, Bowers DC, Ho CY, Hutchins GD, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. *Lancet Oncol* 2012;13:1218–24.

Sasongko TH, Ismail NFD, Zabidi-Hussain Z. Rapamycin and rapalogs for tuberous sclerosis complex. *Cochrane Database Syst Rev* 2016;7:CD011272.

Sbidian E, Hadj-Rabia S, Riccardi VM, Valeyrie-Allanore LL, Barbarot S, Chosidow O, et al. Clinical characteristics predicting internal neurofibromas in 357 children with neurofibromatosis-1: results from a cross-selection study. *Orphanet J Rare Dis* 2012;7:62.

Tucker T, Wolkenstein P, Revuz J, Zeller J, Friedman JM. Association between benign and malignant peripheral nerve sheath tumors in NF1. *Neurology* 2005;65:205–11.

Weiss B, Widemann BC, Wolters P, Dombi E, Vinks A, Cantor A, et al. Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a neurofibromatosis Clinical Trials Consortium phase II study. *Neuro Oncol* 2015;17:596–603.

Immunoglobulin E—Selective Immunoabsorption Reduces Peripheral and Skin-Bound Immunoglobulin E and Modulates Cutaneous IL-13 Expression in Severe Atopic Dermatitis

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Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IA, immunoabsorption; Ig, immunoglobulin; SD, standard deviation

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TO THE EDITOR

Elevated immunoglobulin (Ig) E levels may interfere with skin inflammation in atopic dermatitis (AD) at different levels. One hypothesis is that IgE binding to dendritic cells via the high-affinity IgE receptor, FcεRI, activates

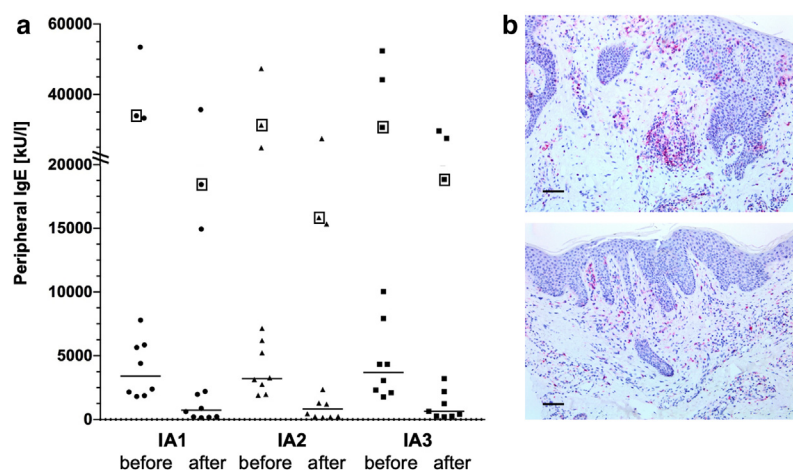


Figure 1. Peripheral and cutaneous immunoglobulin E levels. (a) Effects of extracorporeal immunoadsorption with a single-use immunoglobulin E–selective absorber column on peripheral levels of immunoglobulin E before and after three cycles performed several weeks apart. (b) Example of immunoglobulin E staining of a biopsy taken from a representative eczematous lesion before (baseline; upper picture) and 4 weeks after the third immunoadsorption cycle (picture below). Scale bars = 100 μm. The peripheral immunoglobulin E values of this patient (Patient 9; clinical responder) are marked in (a) with a rectangle. IA, immunoadsorption; Ig, immunoglobulin.

the release of pro-inflammatory mediators and facilitates stimulation of allergen-specific cutaneous T-cell responses (Reich et al., 2001; Werfel et al., 2015). In a pilot trial, extracorporeal immunoadsorption (IA) with columns that bind all Ig classes reduced parameters of cutaneous inflammation and improved the clinical phenotype of AD (Kasperkiewicz et al., 2011). In a subsequent trial with 50 recalcitrant AD patients, pan-Ig IA was compared with IgE-selective IA; both procedures strongly reduced peripheral IgE levels and showed similar clinical effects,

with approximately half of the patients achieving an Eczema Area and Severity Index (EASI) 50 response (Reich et al., 2016). There was evidence that IgE-selective IA was better tolerated, as there were five infectious adverse events, three of them severe, among 24 patients in the pan-Ig IA compared to none in the IgE-selective IA group, in which peripheral IgG levels remained largely unchanged. In these and other reports, IgE-selective IA was carried out with reusable columns, with individual patients receiving up to five repetitive cycles of 3–5 days, each applied

several weeks apart (reviewed by Kasperkiewicz et al., 2018). Although clinical responses occasionally lasted for many months after the last IA (Reich et al., 2016), single-day retreatments on an outpatient basis will be a likely requirement to achieve long-term control in severe cases.

In this open-label pilot trial, we tested the IgE-removing capacity of a single-use IgE-specific column (IgEnio; Fresenius Medical Care, Bad Homburg, Germany). The column is based on a single-chain variable fragment, ScFv12, which is specific for IgE, does not cross-link IgE on mast cells and basophils, and is produced in *E. coli* under Good Manufacturing Practice conditions (Lupinek et al., 2009). Biopsies taken from eczematous target lesions before and after IA were investigated by routine dermatopathology (spongiosis, acanthosis, hyperkeratosis), immunohistochemistry (CD1a, CD3, CD11c, IgE, HLA-DR, Ki-67, IL-17A), and quantitative reverse transcriptase PCR (IL-4, IL-13, IL-17A, IFN-γ) (Reich et al., 2015) (see also [Supplementary Repository](#) online). The study was approved by the Ethical Committee of the Medical Association, Hamburg, Germany, and written informed consent was obtained from all patients.

Eleven patients (mean age 40.3 years; range 29–67 years) with severe recalcitrant AD (mean ± standard deviation [SD] baseline EASI 25.9 ± 11.3, objective Severity Scoring of Atopic Dermatitis Index 49.0 ± 11.6; Dermatology Life Quality Index 15.2 ± 4.5; and Patient-Oriented Eczema Measure 20.9 ± 4.1; and mean ± SD disease duration 31.1 years ± 11.7 years) with largely elevated peripheral IgE levels (13,881.6 kU/l; range 1,811–53,447 kU/l) were treated with three cycles of extracorporeal IgE-selective IA (3–3–2 days) over a period of approximately 6–9 weeks in an open-label pilot trial (see [Supplementary Repository](#)). All patients had been treated with systemic therapies before (including corticosteroids, cyclosporine, azathioprine, and alitretinoin), but did not receive systemic therapy for at least 4 weeks before IA. Topical therapies, including low- to mid-potent corticosteroids and calcineurin inhibitors, were allowed and were kept stable or reduced during IA.

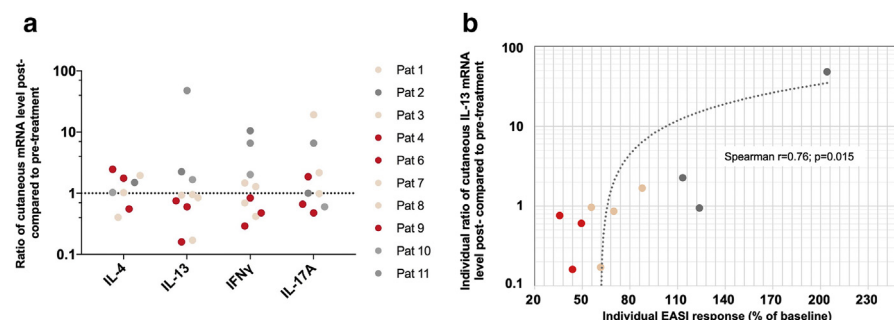


Figure 2. Cutaneous cytokine expression and clinical response. (a) Ratio of cutaneous mRNA levels as determined by quantitative reverse transcriptase PCR in biopsies taken approximately 1 month after immunoadsorption compared to biopsies taken at baseline. A ratio of 1 corresponds to no change in response to immunoglobulin E–selective immunoadsorption, ratios >1 indicate increased, values <1 decreased expression (logarithmic scale). (b) Individual correlation of Eczema Area and Severity Index response (x-axis) and change of cutaneous IL-13 mRNA expression (y-axis, logarithmic scale). Colors of the circles represent clinical responses; red, patients with Eczema Area and Severity Index 50 response; light red, patients with improvement but not Eczema Area and Severity Index 50; gray, patients with no improvement or worsening of immunoadsorption. No biopsies were available from patient no. 5. Pat, patient.

Primary endpoint was the reduction of peripheral IgE at the end of the third IA compared to baseline. All other endpoints and biopsies were assessed approximately 1 month after the third IA and compared to baseline. After three cycles with single-use columns, peripheral IgE levels were significantly reduced to $30.4\% \pm 18.5\%$ ($P = 0.001$, Wilcoxon matched-pairs signed rank test; Figure 1a), while peripheral IgG levels remained largely unaffected (data not shown). Three patients achieved an improvement of at least 50% of their baseline EASI (EASI 50 response; mean $\pm$ SD decrease $56.7\% \pm 6.9\%$), five patients improved, but did not achieve EASI 50 (partial response, mean $\pm$ SD decrease $34.1\% \pm 13.8\%$), two patients showed no change in clinical activity, and one patient worsened (non-response, mean $\pm$ SD increase $47.2\% \pm 49.7\%$). EASI reductions were generally reflected by improvements of other outcome parameters, including objective Severity Scoring of Atopic Dermatitis Index, Dermatology Life Quality Index, Patient-Oriented Eczema Measure, pruritus, and sleep disturbance. Extracorporeal IA with single-use columns was well tolerated and no infectious or serious adverse events were observed. Only patients with EASI 50 response showed consistent reductions of skin-infiltrating CD3⁺ T cells and CD11c⁺ cells ($P = 0.012$ and $P = 0.034$, respectively, Stuart–Maxwell test), while numbers of these cells remained largely unchanged or increased in partially responding and nonresponding patients. Similarly, skin-bound IgE and cutaneous IgE⁺ cells (mostly dermal dendritic cells; compare Figure 1b) consistently decreased in responding ($P = 0.044$; Stuart–Maxwell test), but not in partially responding or nonresponding patients. Cellular changes were associated with changes in the expression of T-helper cytokine pathways. Cutaneous mRNA levels of IL-13 and IFN γ clearly decreased in all patients with EASI 50 response during IgE-selective IA ($P = 0.006$ and $P = 0.005$, respectively, Wilcoxon matched-pairs signed rank test), but increased in all nonresponding patients, while partially responding patients showed intermediate effects (Figure 2a). There was a good correlation between the individual clinical response and the reduction of

cutaneous IL-13 mRNA expression (Figure 2b). No consistent pattern was observed with regard to the other immunohistochemical markers or skin mRNA levels of IL-4 and IL-17A.

Our pilot trial indicates that peripheral IgE levels can significantly and selectively be reduced with a single-use IgE-selective absorber column. IgE-reducing effects were more prominent in patients with baseline IgE levels $\leq 6,000$ kU/l (mean $\pm$ SD reduction $81.4\% \pm 9.7\%$) than in patients with baseline IgE levels $> 6,000$ kU/l (mean $\pm$ SD reduction $48.8\% \pm 7.0\%$), however, two of the EASI 50 responders were in the latter group. Overall, the IgE-reducing capacity and clinical efficacy seemed lower than those recently observed in patients treated with reusable IgE-selective columns (Reich et al., 2016), which might be explained by the reduced number of total and per-cycle treatment days and the inclusion of more patients with very high IgE levels in the present study. Although preliminary, the current study provides evidence that the clinical response of severe AD to IgE-selective IA is associated with a reduction of skin-bound IgE and numbers of cutaneous CD11c⁺ cells, which may be explained by the repetitive removal of peripheral IgE and decreased activation of dendritic cell subsets with IgE-binding capacity. We speculate that the reduction of infiltrating T cells and cutaneous IL-13 production results from a subsequent negative modulation of T-helper 2 cell activation. Interestingly, there was also a link between clinical response and downregulation of cutaneous IFN- γ production in line with previous observations that T-helper 1 pathways may also be activated in chronic eczematous lesions (Fujita et al., 2011). In summary, our paper confirms the therapeutic value of IgE-selective IA in some patients with refractory AD. Optimal responses with the single-use columns tested here can probably be expected in patients with baseline IgE levels of up to 6,000 kU/l, but clinical effects may also be seen in patients with excessively elevated IgE that cannot be treated with other IgE-binding modalities (Quist et al., 2013).

CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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REFERENCES

- Fujita H, Shemer A, Suárez-Fariñas M, Johnson-Huang LM, Tintle S, Cardinale I, et al. Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets. *J Allergy Clin Immunol* 2011;128:574–82.
- Kasperkiewicz M, Schmidt E, Frambach Y, Rose C, Meier M, Nitschke M, et al. Improvement of treatment-refractory atopic dermatitis by immunoadsorption: a pilot study. *J Allergy Clin Immunol* 2011;127:267–70.
- Kasperkiewicz M, Schmidt E, Ludwig RJ, Zillikens D. Targeting IgE antibodies by immunoadsorption in atopic dermatitis. *Front Immunol* 2018;9:254.
- Lupinek C, Roux KH, Laffer S, Rauter I, Reginald K, Kneidinger M, et al. Trimolecular complex formation of IgE, FcεRI, and a recombinant nonanaphylactic single-chain antibody fragment with high affinity for IgE. *J Immunol* 2009;182:4817–29.

Reich K, Heine A, Hugo S, Blaschke V, Middel P, Kaser A, et al. Engagement of the FcεRI stimulates the production of IL-16 in Langerhans cell-like dendritic cells. *J Immunol* 2001;167: 6321–9.

Reich K, Papp KA, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol* 2015;24:529–35.

Reich K, Deinzer J, Fiege AK, von Gruben V, Sack AL, Thraen A, et al. Panimmunoglobulin and IgE-

selective extracorporeal immunoadsorption in patients with severe atopic dermatitis. *J Allergy Clin Immunol* 2016;137:1882–4.

Quist SR, Ambach A, Göppner D, Quist J, Franke I, Bonnekoh B, et al. Long-term treatment of severe recalcitrant atopic dermatitis with omalizumab, an anti-immunoglobulin E. *Acta Derm Venereol* 2013;93:206–8.

Werfel T, Heratizadeh A, Niebuhr M, Kapp A, Roesner LM, Karch A, et al. Exacerbation of atopic dermatitis on grass pollen exposure in an

environmental challenge chamber. *J Allergy Clin Immunol* 2015;136:96–103.



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Altering Perceptions of Scientists among Fifth Graders by the Introduction of Female Role Models: A New Opportunity for Dermatologists?

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TO THE EDITOR

A message from the 2017 Society for Investigative Dermatology's "Irvin H. Blank Forum: Building Team Science: Creating a Culture of Diversity and Inclusion," was that reality and perception may not always match. While scientists come from all gender and racial backgrounds, a child's perception of a scientist may not reflect this. Previous studies have shown that this mismatch is especially prominent with girls, as they predominately have a mental perception of scientists as men (Finson, 2002). This misperception is particularly concerning because it may subconsciously influence future career choices and performance in school. Without young girls taking interest in science, there will be a perpetuation of future pipeline issues for women in science and medicine, affecting retention and advancement. The root cause may stem from traditional stereotype exposure from the media and absence of personal interactions with scientists. While children are less likely to be exposed to traditional scientists outside of the classroom, dermatologists may have an opportunity to influence this area because many children visit dermatologists and many dermatologists are women (Peckham, 2017). By

representing an alternate image of the traditional scientist, it may be possible to influence a future generation.

Caroline Simard, at the Society for Investigative Dermatology's 2017 annual meeting, presented an interesting method to assess children's perspective of scientists. Because children are still in the process of developing their communication skills, they may find it difficult to convey their thoughts through verbal communication alone. The Draw-A-Scientist Test (DAST) and the Draw-A-Scientist Test Checklist (DAST-C) evaluate children's perspectives of scientists by asking them to "draw a picture of a scientist doing science" (Chambers, 1983; Finson et al., 1995). Seven attributes of a standard stereotypical scientist are each assigned a point if present in the picture: lab coat, eyeglasses, facial hair, symbols of research, symbols of knowledge, products of technology, and relevant captions. The DAST-C later improves inter-rater reliability and objectivity by introducing a standard checklist, as well as adding eight new variables: male gender, Caucasian, indications of dangers, presence of light bulbs, mythic stereotypes, indications of secrecy, scientists working indoors, and elderly scientists. The greater the

total score, the greater the drawing represented a stereotypical scientist.

Early in the 2016–2017 school year, one of the authors, a female scientist, hosted a day-long interactive botany session for the fifth graders at a local school. She was assisted by a male student and a female botanist. The students learned about herbarium specimens and complemented their learning by collecting plants from the school garden and pressing them for drying. They also participated in activities, such as using a dichotomous key to differentiate between different types of plants. We hypothesized that exposure to the female scientist may have influenced the fifth graders' impression of scientists. Rather than interview the students, we told their science teacher about the DAST. She was intrigued with the idea and gave a class assignment patterned after DAST at the end of the 2016–2017 school year.

To explore our hypothesis, we performed a retrospective analysis of the drawings. Because of the de-identified nature, the Emory Institutional Review Board deemed this analysis as non-human subjects research. The students self-identified as boy or girl, but did not write any other identifying information. Two raters analyzed the drawings using the DAST-C, and an inter-rater reliability score was calculated using Pearson's correlation coefficient. We compared scores using Generalized Estimating Equation models and

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