of atopic dermatitis remained highest in children with early, persistent atopic (25%) compared with the other 2 groups (16.2% and 8.7%, respectively).

This study shows that our intervention measures were highly effective in preventing asthma in children in this high-risk cohort who had not developed atopy by age 1 year by decreasing the rates of asthma symptoms such as wheeze and not through an allergic/atopic mechanism. Another striking finding of this study is the very high prevalence of asthma at age 7 years in children with early, persistent atopy. This subgroup of children was at high risk of developing asthma and atopic dermatitis as part of the ''atopic march'' regardless of our intervention program. Therefore, being atopic by age 1 year appears to be an extremely important marker for subsequent development of asthma.[5-7]

We have not been able to identify which environmental exposure could explain the results. Because our study was designed to determine the effectiveness of a multifaceted intervention program, the sample size based on such a study design does not permit us to determine which component of the intervention program was useful. As well, it is possible that prenatal exposures may affect on the immune system and lung development and influence expression of disease postnatally. Our finding of the differential effect of intervention measures on asthma and atopy suggests that the pathogenesis of asthma is different from that of other atopic disorders. However, because of the relatively small sample of high-risk children studied, these observations should be confirmed in a larger population-based cohort. Genetic studies may help define better the factors critical to this process among those children who have a strong immediate family history of asthma and atopy.

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Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels

To the Editor:

In a preliminary experience with a limited patient number, we observed surprising success with low-dose anti-IgE therapy in selected adult patients with generalized atopic eczema and high levels of total IgE.[1] This therapeutic improvement was paralleled by a decrease in the mRNA ratio for IgE/IgG in the patients' PBMCs. We now have extended our analysis to a total group of 11 adult patients with severe generalized atopic eczema (3 of these patients have been reported previously).

All patients displayed total serum IgE values far above 1000 IU/mL and had a history of allergic rhinoconjunctivitis and allergic asthma (see Table E1 in this article's Online Repository at www.jacionline.org). All patients had undergone at least 1 standard therapy (systemic corticosteroids, cyclosporine A, UV treatment) before enrollment but were free of systemic treatment for at least 6 weeks before inclusion. All patients, regardless of their IgE values, were treated with a fixed schedule of 10 cycles of 150 mg omalizumab (Xolair; Novartis, Nürnberg, Germany) subcutaneously in 2-week intervals. Before each visit, Scoring Atopic Dermatitis (SCORAD)[2] and a detailed photo documentation were taken. Patients were allowed to use prednicarbat creme as concomitant treatment but were advised to restrain from any additional systemic treatment. All patients agreed to the withdrawal of 10 mL of blood for serum sampling at every visit and to withdrawal of 50 mL of blood for PBMC analysis at the beginning and end of treatment. Serum immunoglobulins, isolation of mRNA, and quantitative PCR to target immunoglobulin-specific transcripts were carried out as documented previously.[1] To use a second investigator-independent parameter for atopic eczema, we looked for changes in thymus and activation-regulated chemokine (TARC/CCL17) levels[3,4] in the serum during therapy as recommended by the manufacturer (Shionogi Research Laboratories, Osaka, Japan).

Low-dose omalizumab was well tolerated in all patients without signs of adverse reactions.

Of the 11 patients, 2 patients responded with a very good clinical response (SCORAD reduction of more than 50%), 4 patients showed satisfying results (SCORAD reduction between 25% and 50%), 3 patients showed clinically no relevant changes (reduction or increase in SCORAD of less than 25%), and 2 patients showed a deterioration of their eczema (SCORAD increase of more than 25%) (Fig 1, *A*). TARC levels showed a reduction of more than 50% in 2 patients (both of which also responded clinically), a reduction

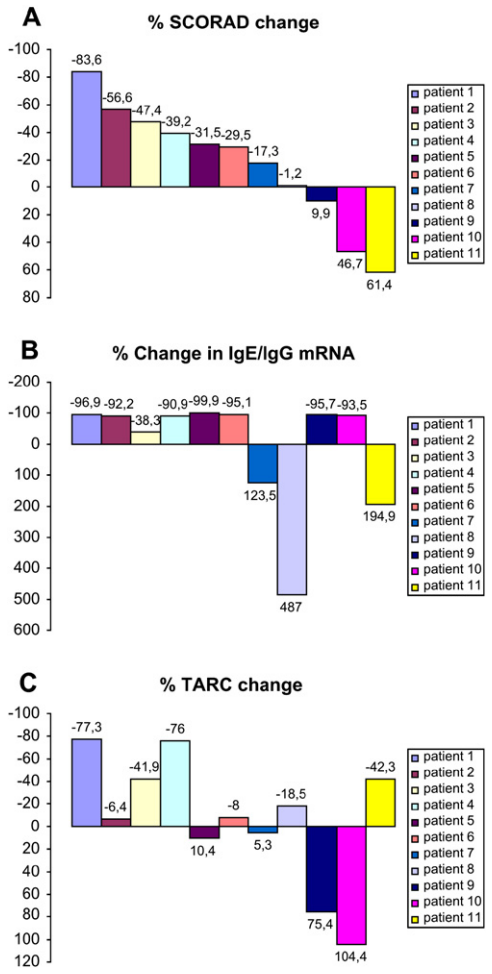

FIG 1. Patient-specific changes in SCORAD **(A)**, ratio of IgE/IgG mRNA **(B)**, and TARC level **(C)**. The calculation of mRNA ratios is based on the totality of transcripts for IgM, IgG, and IgE and is expressed as a percentage ratio of the respective immunoglobulin transcripts.[9] Positive clinical findings (reduction in SCORAD, TARC levels, and IgE/IgG mRNA) are presented in the upper part of the y-axis.

of 25% to 50% in 2 patients (of whom 1 responded clinically well), no relevant changes (below 25%) in 5 patients, and a relevant increase (more than 25%) in 2 patients, all of whom showed either a clinical deterioration or no changes in SCORAD (Fig 1, *C*). The ratio of IgE-specific to IgG-specific transcripts decreased in 8 patients, of whom 6 patients also showed good clinical improvement (accounting for the totality of patients responding to omalizumab), 1 patient showed no clinical change, and 1 patient showed a relevant increase in SCORAD level. The IgE/IgG mRNA ratio increased in 2 patients showing no clinical changes after omalizumab therapy and in 1 patient who relevantly deteriorated under therapy (Fig 1, *B*). As observed previously, total IgE (bound and free IgE) slightly increased during therapy, whereas free IgE remained basically stable over the treatment period. Total serum IgM and total serum IgG showed no major changes in the analyzed patients (data not shown).

Of note, the changes observed in our limited number of analyzed patients have to be evaluated in the context of known percentages of placebo-induced clinical improvement in atopic eczema patients undergoing clinical trials. This percentage has been described to be as high at 40%. Therefore, the observed outcome in our omalizumab trial might not entirely reflect drug-associated clinical changes. In line with this observation, the cases showing deterioration of their skin conditions under anti-IgE, in our eyes, most probably experienced spontaneous flare-ups, which were not controlled/cured by omalizumab, rather than presenting a true drug-induced negative effect.

Our current study extends the previously published reports on omalizumab in atopic eczema by integrating laboratory data in the follow-up of treated patients. The clinical improvements during the 20-week treatment period in 6 of 11 patients support data showing good clinical response in selected patients.[5] Similar to these patients, we have used omalizumab in a much lower dosage than required for the complete removal of IgE from the circulation. In fact, only a very small proportion (probably between 1% and 5 % of all serum IgE molecules) in our patients was bound by omalizumab. It is therefore very unlikely that the reduction in free serum IgE accounted for the clinical response. Alternatively, molecular changes such as the observed switch to reduced IgE mRNA production could mirror a clinical outcome.

The parameter used to identify responders in our previous publication,[1] namely the changes in IgE/IgG mRNA, showed association with a positive clinical course but failed to identify all patients without clinical improvement.

Of note, the reported number of 11 patients can only be considered as a pilot investigation without the power to draw statistical conclusions. However, the changes in IgE/IgG mRNA turned out to identify better patients with a good or satisfying clinical response as compared to serum TARC levels, a parameter that has been suggested recently by researchers as being suitable in the follow-up of generalized atopic eczema patients.[4]

One of the most striking findings of our current study and our previous work is the fact that despite dramatic changes in the mRNA level for the different immunoglobulins (see Table E1), the amount of serum immunoglobulins did not change substantially during the treatment period. One explanation for this discrepancy could be that most immunoglobulins are not produced in PBMC plasma cells but by long-living plasma cells residing in the bone marrow.[6] In addition, the thorough analysis of the transcriptional changes revealed that besides the mRNA for secreted form of the immunoglobulins, the membrane-type, immunoglobulin-specific mRNA also increased during omalizumab therapy (data not shown). This increase plays most likely a role for IgG (which was found increased in most patients) rather than for IgE, which is an immunoglobulin in which the membrane-type encoding mRNA is not processed properly.[7] From our data, decreases in the mRNA ratio for IgE/IgG more than for IgE alone would be a promising marker to identify individuals responding to omalizumab treatment. However, this marker will have to be confirmed in larger cohorts.

As a summary of our clinical observations and in response to the good safety data[8] being reported for this antibody, we think that our pilot data might warrant the exploration of omalizumab in patients with generalized atopic eczema under controlled study conditions. In our eyes, this antibody does not have to be dosed to completely remove IgE from serum.

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