

All patients using off-label medication must be informed about the legal consequences, read the manufacturer's consumer information, discuss it with their doctor and give written informed consent.

Goethe Universität, Frankfurt am Main, Germany L.M. DICKMANN
Brasenose College Oxford, Radcliffe Square, J.R.M. DICKMANN
Oxford OX1 4AJ, U.K.

Correspondence: Julian R.M. Dickmann.

E-mail: julian.dickmann@bnc.ox.ac.uk

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Proactive treatment appears to decrease serum immunoglobulin-E levels in patients with severe atopic dermatitis

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MADAM, Atopic dermatitis (AD) is a chronic inflammatory skin disease with a broad spectrum of clinical manifestations.¹ Central to the pathogenesis of AD are immunological dysregulation of T-cell function and, frequently, elevated immunoglobulin (Ig) E levels.² In severe AD, total serum IgE level can be increased up to 10 000 IU mL⁻¹ or even more and may cause several problems in treating allergy.

Recently, proactive treatment, which is long-term, low-dose intermittent application of anti-inflammatory agents to the previously affected skin together with daily application of emollients to unaffected areas, was reported to have several clinical advantages.^{3–7} However, there have been no published

reports regarding the relationship between IgE level and a proactive treatment approach to AD.

To investigate whether proactive treatment changes serum IgE level or not, we conducted a retrospective study of patients with moderate to severe AD who were treated and followed up in the Division of Allergy, National Center for Child Health and Development (Tokyo, Japan). The inclusion criteria were: (i) admission between January 2004 and July 2007; and (ii) an IgE level above 100 IU mL⁻¹ at the first visit, with re-evaluation at least once more after 1–2 years.

In the remission–induction phase, patients applied topical corticosteroids twice daily every day to all affected body areas until visible inflammation disappeared. The maintenance phase consisted of proactive intervention using topical corticosteroids after twice daily skin washing and continuous environmental control: 0.12% betamethasone valerate was applied to the body and extremities, 0.1% hydrocortisone butyrate on the face. According to the tapering protocol of our division (Fig. S1; see Supporting information), the patients were advised to use topical corticosteroids intermittently and proactively on all previously identified affected areas. None of the patients received any additional systemic therapy.

If the patient maintained proactive therapy for 2 years, he or she was assigned to the 'proactive treatment group'. If the patient discontinued the recommended proactive treatments and treated symptoms reactively, he or she was assigned to the 'reactive treatment group'.

Scoring Atopic Dermatitis (SCORAD),⁸ safety assessments and height measurements were performed at each hospital visit. Serum total IgE and food-specific IgE levels using an ImmunoCAP Specific IgE kit (Phadia AB, Uppsala, Sweden) were evaluated.

Forty-five patients satisfied the inclusion criteria. All patients achieved remission within 1–2 months of in-hospital treatment. Twenty-five patients continued twice-a-day skin care and proactive treatment and were assigned to the proactive treatment group. Twenty patients failed to continue proactive treatment and were assigned to the reactive treatment group (Fig. S2; see Supporting information). The mean age $\pm$ SD was 4.3 $\pm$ 3.3 years (proactive group) vs. 5.0 $\pm$ 4.0 (reactive group). Baseline SCORAD median (interquartile range) was 82.2 (68.2–85.6) vs. 79.5 (66.8–91.4). Baseline total IgE was 2442 (1263–8330) IU mL⁻¹ vs. 2081 (1059–6980). All parameters measured did not show significant differences (Table S1; see Supporting information), but the mean worst SCORAD in the proactive group was lower than that in the reactive group. The application frequency of topical steroid necessary to maintain a clear status was titrated in the proactive group patients, usually 1 day in a week (48% of the proactive group) or 2 days in a week (also 48%).

Serum IgE titre was significantly decreased in the proactive treatment group compared with the reactive treatment group ($P < 0.01$, Mann–Whitney U-test, Fig. 1). In addition, the food-specific IgE level was significantly decreased in the pro-

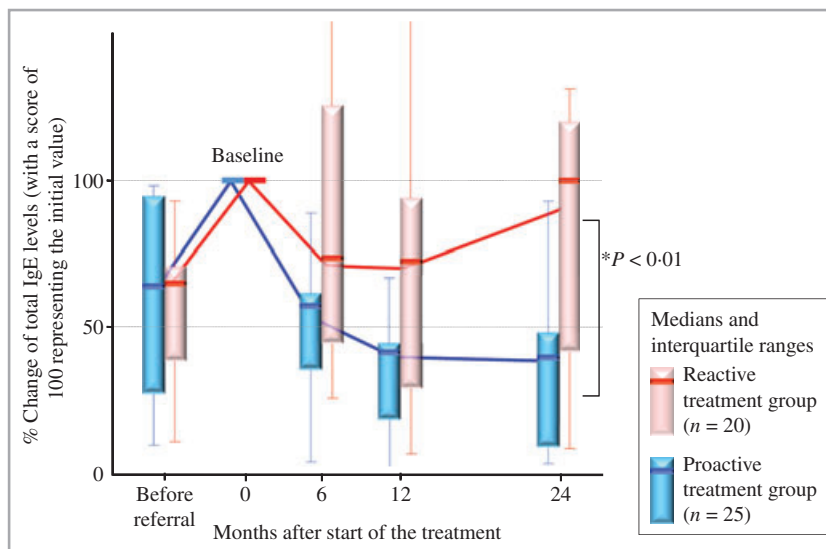


Fig 1. Percentage changes of total immunoglobulin (Ig) E levels during the treatment. Baseline (just before the start of inpatient treatment) total IgE of each patient was determined as 100%. In the proactive group, the total IgE level was reduced by our comprehensive treatment and IgE levels at 2 years after treatment commencement were significantly lower than in the reactive group. *Significant differences between the two groups after 2 years ($P < 0.01$, Mann–Whitney U-test).

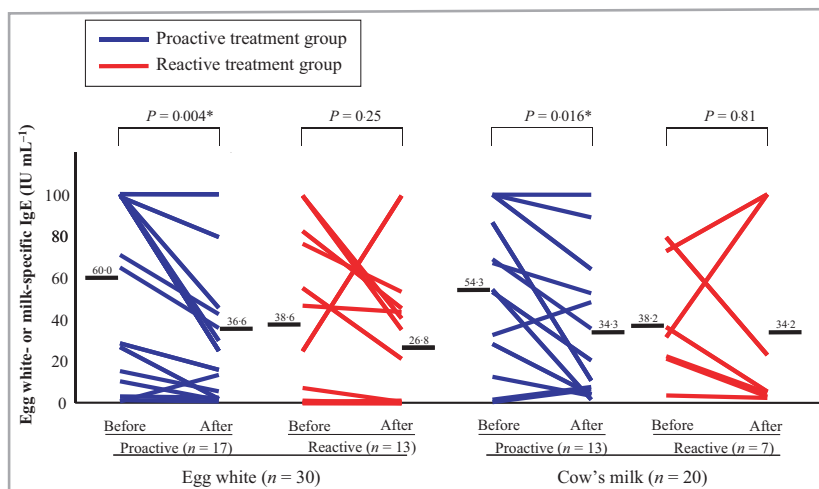


Fig 2. Changes in egg white- and milk-specific immunoglobulin (Ig) E levels after the start of treatment. Food-specific IgE levels in the patients in the proactive treatment group (blue line) decreased significantly during follow-up. No significant decreases were seen in the reactive treatment group patients (red lines). *Significant difference in Wilcoxon signed rank test.

active group compared with the reactive group (Wilcoxon signed rank test, Fig. 2).

There were no serious adverse events in any of the patients during treatment. Eight patients (32%) in the proactive treatment group experienced fungal infection (two patients in reactive group). Skin thinning and striae formation were not seen in any patients. Hypertrichosis was suspected in some patients before titration of frequency of topical steroid, but normalized when the frequency of topical steroid was decreased to twice a week or less. The mean height velocity SD score was relatively high in both groups and did not show any difference.

Inflamed skin of AD bears several kinds of inflammatory cells, including T-helper 2 cells which produce interleukin (IL)-4 and IL-13 and lead to production of IgE in cooperation with B cells. IgE might be synthesized in inflamed skin, its regional lymph node and elsewhere in the body. One can imagine that suppression of inflammatory cells in the skin could lead to disruption of the IgE synthesis mechanism.

We used proactive therapy for the management of severe AD and the serum IgE level appeared to decrease. Continuous close adherence to the proactive treatment may suppress inflammatory cells and lower the serum IgE level. Decrease of egg white- and milk-specific IgE levels was also seen, and may play an important role in alleviating food allergies. This is the first report to evaluate the effectiveness of proactive therapy in reducing the serum IgE level.

Because this study was retrospective and was designed using therapy adherence as a discriminating factor for assigning the patients, we hope to execute a prospective randomized controlled trial. We also want to understand the mechanism to decrease serum IgE and to change the clinical course of food allergy.

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Division of Allergy, National Center for
Child Health and Development, Tokyo, Japan
Correspondence: Ichiro Nomura
E-mail: nomura-i@ncchd.go.jp

T. FUKUIE
I. NOMURA
K. HORIMUKAI
A. MANKI
I. MASUKO
M. FUTAMURA
M. NARITA
T. OHZEKI
K. MATSUMOTO
H. SAITO
Y. OHYA

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Key words: atopic dermatitis, food allergy, immunoglobulin E, proactive therapy, topical corticosteroid

Conflicts of interest: none declared.

Supporting information

Additional supporting information may be found in the online version of the article:

Fig S1. Our standard protocol for proactive treatment of atopic dermatitis.

Fig S2. Patient flow.

Table S1. Stratified analysis of the two groups.

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An unusual case of granulomatous cutaneous T-cell lymphoma showing subcutaneous/muscular involvement and a 5q33.1 deletion

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MADAM, Granulomatous slack skin (GSS) and granulomatous mycosis fungoides (GMF) are classified as subtypes of mycosis fungoides (MF) according to the recent classifications of haematolymphoid tumours.^{1,2} GSS clinically manifests as bulky, infiltrated folds of lax skin in flexural areas, histologically characterized by a granulomatous T-cell infiltrate with abundant macrophages, multinucleated giant cells and loss of elastic fibres.³ We describe an unusual case of granulomatous cutaneous T-cell lymphoma (CTCL) clinically presenting without typical MF cutaneous lesions and showing histopathological features consistent with GSS, with the absence of elastolysis. Array-based comparative genomic hybridization (aCGH) was also performed showing a unique loss of 5q33.1.

A 34-year-old white man presented with a 5-year history of isolated, deep and painful nodules, rapidly enlarged and localized on the right part of the trunk (Fig. 1a), on the right buttock, on the left thigh (Fig. 1b), left knee and left shoulder. A complete physical examination did not reveal any MF-like typical aspects or lymph node enlargement. His medical and family history was unremarkable. Two previous cutaneous biopsies were not diagnostic for CTCL.

When he presented to us, another biopsy was taken from a skin lesion, and previous histological specimens were reviewed. They showed a focal granulomatous lymphoid infiltrate localized in the dermis and hypodermis (Fig. 1c) and a dense lymphoid infiltrate containing multinucleated giant cells (Fig. 1d) forming granulomas in the subcutis and fascia (Fig. 1e). The atypical proliferating lymphocytes showed small to medium-sized cerebriform and hyperchromic nuclei, typically surrounding the multinucleated giant cells and forming rosette-like features (Fig. 1f); there was also evidence of mild lymphophagocytosis. Immunohistochemically, tumour cells were CD2++, CD3+ (Fig. 2a), CD4+, CD5+/-, CD7-, CD8-, CD30-, CD45RO+, interleukin (IL)-17- and Ki-67+ (Fig. 2b). Multinucleated giant cells were positive for IL-17 (Fig. 2c), interferon (IFN)- γ , tumour necrosis factor (TNF)- α , CD68 and CD163 markers.

Molecular analysis revealed a monoclonal T-cell receptor- γ gene rearrangement (primer V2a, V1-8). A histological diagnosis of GSS was made. Complete haematological staging revealed no abnormalities. Magnetic resonance imaging and a thoracoabdominal computerized tomography scan of the cutaneous lesions showed involvement of only subcutaneous tissue and the muscular layer by the infiltrate.

Genotypic studies of the skin biopsy by aCGH showed a loss of only 5q33.1 containing the IL17B and PCYOX1L genes