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Cyclosporin A (CyA) reduces sCD30 serum levels in atopic dermatitis: a possible new immune intervention

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Key words: atopic dermatitis; cyclosporin A; sCD30; Th2 immune response.

Atopic dermatitis (AD) is a chronic inflammatory skin disease frequently associated with asthma, rhinitis, and food allergy. Lymphocytes producing Th2-type cytokines (such as interleukin [IL]-3, IL-4, and IL-5) have been thought to have a key role in the pathogenesis of the disease. We have recently demonstrated that elevated serum levels of the soluble form of CD30 (sCD30), an activation marker of Th2-cell clones, correlates with disease activity in pediatric patients suffering from AD. Clinical trials have demonstrated that cyclosporin A (CyA) treatment resulted in significant improvement of clinical symptoms in patients affected with AD. In this study, we evaluated the role of CyA in modulating sCD30 release in a group of adult patients affected by severe AD treated with CyA at the dosage of 3.5 mg/kg body weight for 12 weeks. Our results demonstrated, in parallel with an improvement of clinical symptoms, a significant reduction of serum levels of both IL-4 and sCD30, thus suggesting that CyA can prevent the activation of Th2 cells observed in AD.

Atopic dermatitis (AD) is a chronic inflammatory skin disease frequently associated with asthma, rhinitis, and food allergy (1, 2). Patients often have eosinophilia and high IgE levels and show prick-test positivity to a wide range of aero- and food allergens (3). In this clinical condition, lymphocytes producing Th2-type cytokines (such as interleukin [IL]-3, IL-4, and IL-5) have been thought to have a key role. Spontaneous release of IL-4 and IL-5 has been demonstrated in supernatants of both peripheral blood lymphocytes and cells infiltrating lesional skin (4, 5). It is now accepted that IL-4 is essential for encouraging IgE production, whereas IL-3 and IL-5 enhance eosinophil proliferation and function. Recently, it has been reported that CD30, a 120-kDa

Date:

Accepted for publication 3 December 1998

To cite this article:

Bottari V., Frezzolini A., Ruffelli M., Puddu P., Fontana L., De Pità O. Cyclosporin A (CyA) reduces sCD30 serum levels in atopic dermatitis: a possible new immune intervention.
Allergy 1999; 54: 507–510.

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ISSN 0105-4538

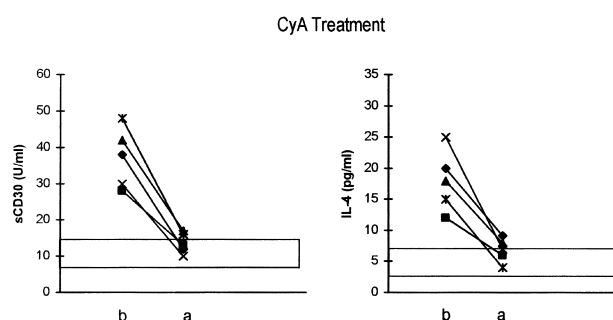


Figure 1. Reduction of sCD30 and IL-4 serum levels in group of AD patients ($n=5$) treated with CyA. b: before CyA treatment, a: after CyA treatment, □: normal range ($n=10$).

membrane-bound glycoprotein belonging to the TNF-NGF superfamily, is an activation marker of T-cell clones, showing a Th2-like cytokine profile (6, 7). The soluble form of the molecule (sCD30) is released into the bloodstream after cellular activation, and it is considered a marker of several Th2-related disorders (8). Furthermore, we have recently demonstrated that elevated serum levels of sCD30 correlate with disease activity in pediatric patients suffering from AD (9). In the last few years, some clinical trials have demonstrated that treatment with cyclosporin A (CyA) resulted in significant improvement of clinical symptoms in patients with AD (10–12). In this regard, we decided to investigate the possible role of CyA in modulating sCD30 release in a clinical condition associated with an evident Th2 imbalance, selecting a group of adult patients affected by severe AD with extremely high levels of IgE.

Material and methods

Patients

Ten adult patients suffering from severe AD and having extremely high serum levels of IgE were selected for the study. The patients were also affected by asthma, rhinitis, and food allergy. The AD involved large cutaneous areas (SCORAD index: 82 ± 12). The mean serum IgE level was $23\,100 \pm 2\,500$ kU/l, and the eosinophil count ranged from 820 to 1160×10^3 cells/ μ l. All patients underwent cutaneous prick test and RAST with a panel of common aero- and food allergens, testing positive for several of them.

Immunologic evaluation

Immunologic soluble parameters, such as sIL-2R (T Cell Diagnostic, Woburn, MA, USA), interferon-gamma (IFN- γ)

(R&D System, MN, USA), IL-4 (IPR, Catania, Italy), sCD23 (T Cell Diagnostic, Woburn, MA, USA), and sCD30 (DAKO, Glostrup, Denmark) were evaluated in serum samples with commercially available ELISA kits, according to the manufacturers' instructions. All serum samples, stored at -80°C until use, were assayed in duplicate. Ten serum samples from healthy adult donors, without any history of atopy, were assayed as controls.

Treatment

Patients were subdivided into two groups: five receiving CyA at a dosage of 3.5 mg/kg body weight for 12 weeks, and five receiving local therapy alone with corticosteroids (budesonide 0.025% b.i.d.) and emollient cream.

Statistical analysis

Statistical analysis was performed with unpaired and paired Student's *t*-test, and differences associated with probability values of $P < 0.05$ were considered to be significant.

Results

All patients with AD showed significantly higher serum levels of sIL-2R (1920 ± 220 vs 627 ± 174 U/ml, $P < 0.0001$), IL-4 (23 ± 6 vs 4 ± 2 pg/ml, $P < 0.0001$, sCD23 (9.2 ± 2 vs 2.1 ± 1 IU/ml, $P < 0.0001$), and sCD30 (52 ± 12 vs 10 ± 5 U/ml, $P < 0.0001$) than normal donors. Serum levels of IFN- γ were undetectable in all AD subjects. All patients obtained complete remission of AD manifestations and a reduction of SCORAD index after treatment (25 ± 14). Furthermore, the group of patients treated with CyA showed an improvement of some immunologic parameters. In addition to a reduction of eosinophil count to $550 \pm 100 \times 10^3$ cells/ μ l and of sIL-2R (1120 ± 112 vs 800 ± 53 , $P < 0.0001$), we observed a significant decrease of both IL-4 (18 ± 5 vs 6.8 ± 2 pg/ml, $P < 0.005$) and sCD30 (38 ± 8 vs 13.6 ± 2.8 U/ml, $P < 0.002$) serum levels (Fig. 1), while sCD23 and IgE levels were unchanged. However, no significant modification of either IL-4 or sCD30 was detected in patients treated with topical therapy alone (Fig. 2).

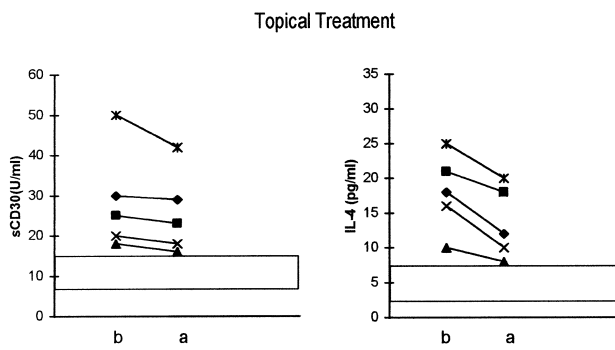


Figure 2. Serum levels of sCD30 and IL-4 remained unchanged in group of AD patients ($n=5$) treated with topical therapy alone. b: before treatment, a: after treatment, □: normal range ($n=10$).

Discussion

Several publications have demonstrated the presence of Th2-type cytokines in both serum and skin lesions of atopic patients, thus suggesting the involvement of Th2 cells in the pathogenesis of AD (4, 5, 9).

In view of these mechanisms, new immunologic therapies for the treatment of AD are likely to focus on the modulation of Th2 cells and their derived cytokines. CyA is known to be a potent T-cell inhibitor, preventing the production of IL-2, which acts as an autocrine T-cell growth factor. In this light, the beneficial effects of CyA in the treatment of AD have been mainly attributed to the inhibition of T-cell activation; a marked reduction in the number of activated lymphocytes expressing the IL-2 receptor (CD25) has been observed in the blood and in the dermal infiltrate of AD patients after CyA therapy, with a parallel improvement in clinical condition (13). Moreover, it

has been shown that CyA can inhibit the gene expression of IL-3 and IL-4, and, to a lesser extent, of IL-5 (14, 15). Recent publications have reported that CyA can lead to an *in vitro* reduction of IL-4 and a parallel increase in IFN- γ production from stimulated peripheral blood mononuclear cells (PBMC) of childhood AD patients (16). It has been further documented that, both in adult and childhood severe AD, the expression and production of IL-5 from PBMC were significantly reduced during CyA therapy and by the presence of CyA *in vitro*, with a parallel improvement in the disease course (17, 18).

These data account for the reduction of eosinophilia, which is sustained by IL-3 and IL-5, as well as the progressive lowering of serum IgE levels after long-term CyA treatment in AD patients. In this study, we have shown that CyA treatment can reduce high serum levels of sCD30 in AD patients. In our opinion, this information suggests a reduction of cell activation and/or frequency of Th2 cells. This finding may be explained by the capacity of CyA to block the synthesis of IL-2 at transcriptional level, thus preventing CD4⁺ allergen-specific T-cell clones from expanding. It is now accepted that IL-4 is essential for the switching from Th0 to Th2 cells, and that CyA can block IL-4 production by T cells. This probably reduces markedly the subsequent differentiation into Th2 clones.

In conclusion, we suggest that CyA treatment in AD patients can prevent the expansion of Th2 cells, which is one of the main goals of therapeutic strategies in atopic disease, and may aid in the manipulation of the allergic immune response.

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