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An Unexpected Increase in Circulating IFN-γ by Cyclosporin A in Atopic Patients: A Discrepancy between *In vitro* and *In vivo* Events

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Defective interferon γ (IFN-γ) production has been suggested to be relevant to immunologic abnormalities observed in atopic dermatitis (AD). We describe two patients with severe AD who were treated with oral cyclosporin A (Cy-A) and in whom the serum levels of IL-1α, IFN-γ and tumor necrosis factor α (TNF-α) were sequentially measured. Cy-A, known to inhibit IFN-γ production *in vitro*, caused a rapid rise in serum IFN-γ, but not Il-1α and TNFα, levels in the patients and the IFN-γ levels appeared to be inversely related to the therapeutic efficacy. The observed increase in serum IFN-γ levels during Cy-A therapy may have contributed to a marked clinical improvement of the AD. *Key words: Serum cytokine levels; Atopic dermatitis.*

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Several immunologic abnormalities have been demonstrated in atopic dermatitis (AD), including elevated levels of IgE, impaired NK cell activity and decreased suppressor cell function. Recent attention has focused on the cytokine production of patients, and imbalances between the production of interleukin 4 (IL-4) and interferon γ (IFN-γ) have been proposed to explain the elevated IgE and pathological conditions seen in AD (1). An increased frequency of bacterial and viral skin diseases in AD may be partly explained by the defective IFN-γ production (2). However, there are to date few, if any, *in vivo* data to demonstrate the defective IFN-γ production in AD. We describe here two patients with severe AD who were treated with oral cyclosporin A (Cy-A) for up to 8 weeks and in whom the serum levels of IL-1α, IFN-γ and tumor necrosis factor α (TNF-α) were sequentially measured.

METHODS

Cytokine assay

The serum samples were obtained for determination of the serum levels of the cytokines from two patients with severe AD at various time points. The serum levels of the cytokines were determined by sensitive radioimmunoassays as previously described (IL-1α, Amersham Corp., Arlington Heights, IL; IFN-γ, Centocor, Malvern, PA; and TNF-α, Medgenix, Fleurus, Belgium) (3, 4). Our earlier experiments confirmed no cross-reaction of the monoclonal antibodies used in the radioimmunoassays. The lower limits of sensitivity of the assay were 5 fmol/ml for IL-1α, 0.02 U/ml for IFN-γ, and 15 pg/ml for TNF-α.

CASE REPORTS

Case 1

A 45-year-old man had a 20-year history of severe AD refractory to conventional treatment. Systemic therapies had been discontinued 2 weeks prior to treatment with Cy-A. Topical corticosteroid was not interrupted. Treatment with 5 mg/kg/day of Cy-A was begun and clinical improvement was apparent after 1–2 weeks of therapy. Facial lesions responded most quickly and all the lesions essentially resolved after 6 weeks of therapy. As shown in Fig. 1, serum IL-1α levels were not significantly raised above control values (n = 21, median 24.5 fmol/ml, range 17–70) and remained essentially unchanged during the 8-week treatment period, despite a dramatic clinical improvement. Unexpectedly, a rapid rise in serum IFN-γ levels above control values (19 out of 21 below 0.02 U/ml, range <0.02–0.05) was observed after 1 week of therapy. The elevated serum IFN-γ levels were observed throughout the Cy-A treatment period but then gradually declined. In contrast, there is an excellent correlation of clinical improvement and serum TNF-α levels, as previously described in psoriatic patients (4); a significant rise in TNF-α above control values (n = 21, all below <15 pg/ml) was noted before therapy and the levels returned to baseline within 1 weeks of starting Cy-A therapy.

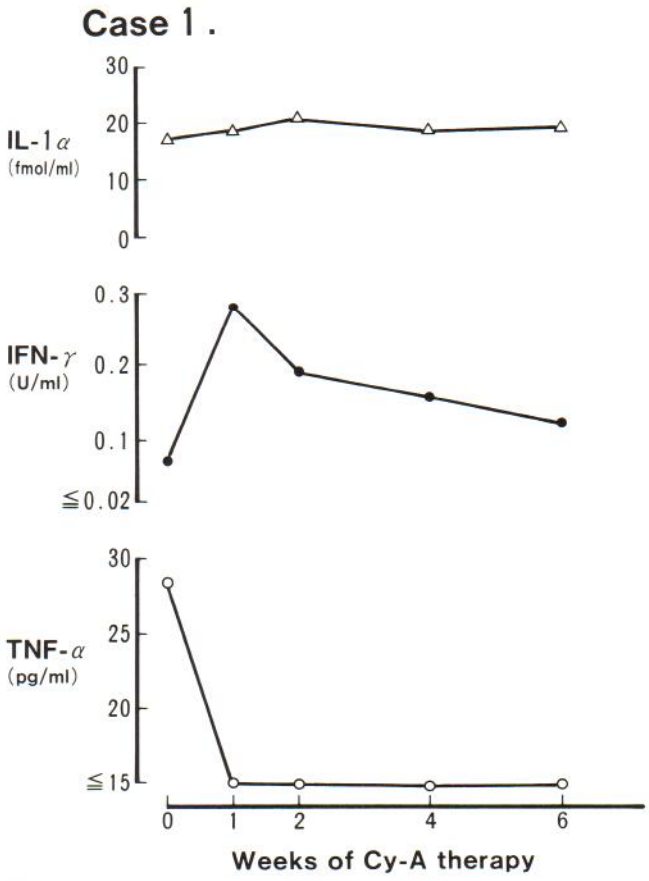

Fig. 1. Serum levels of IL-1α, IFN-γ and TNF-α during Cy-A therapy in Case 1.

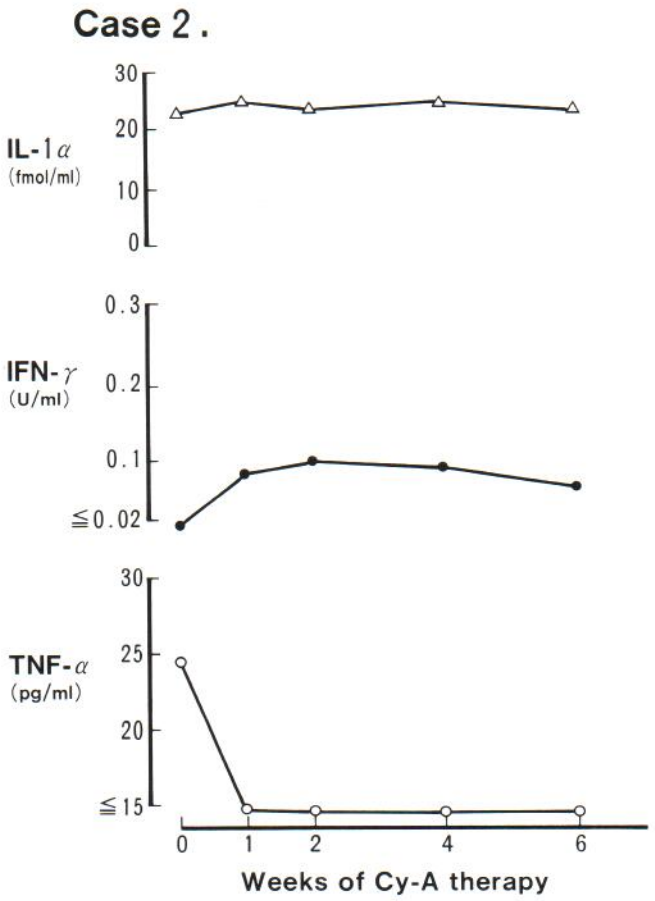

Fig. 2. Serum levels of IL-1α, IFN-γ and TNF-α during Cy-A therapy in Case 2.

Case 2

A 24-year-old man had a 15-year history of severe AD. Two weeks prior to treatment with Cy-A, systemic therapies had been discontinued. Topical corticosteroid was not withdrawn. The patient started receiving Cy-A at a dose of 5 mg/kg/day. Within 4 weeks he had responded, and by 8 weeks all the lesions were in remission, although the efficacy of Cy-a in Case 2 was less dramatic than that in Case 1. As shown in Fig. 2, considerable increases in IFN-γ levels and decreases in TNF-α levels, thought to be attributable to Cy-A therapy, were also observed; they were, however, less prominent than those in Case 1.

DISCUSSION

In our cases, IFN-γ was the only circulating cytokine detected in increased amounts in the sera after Cy-A therapy, and its concentration appeared to be inversely related to the extent of the therapeutic effects observed. Recent studies, however, have clearly demonstrated that Cy-A completely inhibits the production of IFN-γ: the addition of Cy-A *in vitro* to lymphocytes stimulated by mitogens or antigens inhibits the production of IFN-γ (5), and oral Cy-A also inhibits *in vivo* IFN-γ production in psoriasis (4). Thus, there seems to be a discrepancy between our current knowledge of cytokine production derived from *in vitro* work and events that occurred in our cases. In light of the recent observation that clinical improvement was shown during *in vivo* treatment of AD patients with recombinant IFN-γ (6, 7), the observed increase in serum IFN-γ levels during Cy-A thereby may have contributed in part to a marked clinical improvement of the AD. Alternatively, it is also possible that this increase in IFN-γ levels merely represents a consequence of the clinical improvement. Another possibility is that reduction of the daily topical corticosteroid dose after Cy-A therapy may have been reflected in this increase in IFN-γ levels, although the patients claimed to have continued to use corticosteroids as before. This is unlikly, however, since our previous studies demonstrated that IFN-γ levels rapidly returned to baseline levels 1–2 weeks after the initiation of Cy-A therapy in psoriatic patients, who showed a marked clinical improvement similar to the AD patients in this study (4).

Although it remains to be established whether the increase in IFN-γ production seen during Cy-A therapy is intrinsic to T cells from AD patients, our results indicate that Cy-A can modulate the production of cytokines in a way that is distinct from that observed in tissue culture systems, especially when administered to patients with intrinsic immunologic abnormalities, such as AD. Because much of the work on the effects of Cy-A on the production of various cytokines has involved *in vitro* approaches, these apparently contradictory results suggest that there is more to be learned about the *in vivo* production of cytokines and admonish us to be careful in extrapolating the regulation of cytokine production demonstrated in tissue culture systems to *in vivo* situations, especially in disease processes.

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