Bestatin Therapy of Patients with Atopic Dermatitis

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Ten adult patients with severe atopic dermatitis were treated for three months with bestatin, which is a metabolite of Streptomyces olivoreticuli. Bestatin has been shown to increase tumor resistance in mice, augment a variety of immune responses and to reduce the level of IgE in non-atopic healthy persons. During bestatin therapy we were not able to see any clinical change of the atopic dermatitis. No influence was found on the concentration of IgE in serum and the number of eosinophils in blood. The percentage of T lymphocytes and the Con A-induced suppressor cell activity was not changed. (Received June 18, 1983.)

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(2S, 3R)-3-amino-2-hydroxy-4-phenyl-butanoyl-L-leucine, called bestatin, is found in the culture filtrate of Streptomyces olivoreticuli. The substance has a molecular weight of 350 dalton and is a competitive inhibitor of aminopeptidase B and leucine aminopeptidase. These enzymes are found on the cell surface of many cells including lymphocytes. Bestatin augments various immune responses such as increased resistance towards transplanted tumors in mice (1), increased macrophage cytotoxicity for tumor cells in vitro (2), and increased delayed hypersensitivity of the skin (3). Bestatin has therefore been given to patients with cancer, but its clinical efficacy is still unknown.

It was recently observed that bestatin induced a transient reduction in the IgE concentration in serum of healthy, non-atopic persons (4). Patients with atopic eczema have increased levels of IgE in serum and reductions of their immune reactivity (5–8). We have therefore tried bestatin therapy in a group of patients with severe atopic dermatitis.

PATIENTS AND METHODS

Ten patients took part in the study, nine women and one man. Their age ranged between 24 and 61 years, median value 35 years. They suffered from severe atopic eczema of life-long duration. All gave informed consent about their participation in the trial, which was approved by The Committee of Ethics, Aarhus County.

Bestatin was given as tablets 20 mg twice daily for three months. The study was conducted over a
one-year period with two or three participants every fourth month in order to avoid a bias from seasonal variation of disease activity.

The trial was "open" and the clinical evaluation was done monthly by one of us (M. C.). Apart from bestatin the patients received topical steroids without restrictions. All participants completed the trial without any side effects from the drug.

The clinical evaluation was done by giving points for disease activity in five regions (face, arms, hands, legs and body). The scoring was as follows: 0: no skin disease, 1: slight dermatitis, 2: moderate dermatitis, 3: severe dermatitis, and 4: severe dermatitis with excoriations. The points from each region were summarized at every visit. The highest possible score was 20.

Five patients participated in the immunological monitoring, which was performed before and during the treatment period. We measured the number of circulating eosinophils in blood and the concentration of IgE in serum using a radioimmunoassay (Pharmacia; upper normal limit 150 IU per ml of serum). T lymphocytes were determined through rosetting with sheep erythrocytes, which were treated with AET (2-amino-ethyl-isothiouronium bromide hydrobromide) to increase the binding between erythrocytes and T lymphocytes (E-AET). Erythrocytes and lymphocytes were incubated for 4°C for at least one hour before reading. The E-active technique is in principal identical except that the sheep erythrocytes were not treated with AET and the incubation period was only 5 min before resuspension and reading. These assay give a profile of the sheep erythrocyte receptor affinity on T lymphocytes (for further details see ref. 8).

The suppressor cell activity was measured by stimulating lymphocytes for 48 hours with 1 and 50 µg of Concanavalin A per ml. The Con A-stimulated lymphocytes and autologous unstimulated lymphocytes, which had been cultured in parallel ("control cells"), were treated with mitomycin C. They were added 1:1 to autologous lymphocytes ("responder cells"), which had been kept in culture without stimulation for 48 hours. The "responder + suppressor" cells and "responder + control" cells were then stimulated with three different concentrations of phytohemagglutinin (PHA). Suppression was calculated as 1 - (the cumulative response of "responder + suppressor" cells)/(the cumulative response of "responder + control" cells) % (for further details, see ref. 7).

RESULTS

The clinical evaluation of bestatin therapy showed that the drug was not able to change the course of atopic dermatitis (Table I).

The individual serum IgE concentrations are shown in Fig. 1 and the median values for the group in Table I. No significant change occurred. The number of circulating eosinophilic leukocytes in blood was unchanged (Table I).

The percentage of T lymphocytes was not significantly changed. The increase in the percentage of E-active rosette-forming cells was seen in three of five patients. These three patients were started on bestatin therapy during an unusually hot summer, and we saw an identical increase during the observation period in two control persons (results not shown). We feel that the change is a technical variation during a hot summer period.

The non-specific suppressor cell capacity of blood lymphocytes was not altered by

Table I. The results are the median values for five patients with atopic dermatitis, treated for three months with bestatin 20 mg × 2 daily.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>0 months</th>
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<th>2 months</th>
<th>3 months</th>
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<td>10</td>
<td>10</td>
<td>12</td>
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<td>IgE (IU per ml)</td>
<td>4 710</td>
<td>4 980</td>
<td>4 050</td>
<td>4 325</td>
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<td>Eosinophils per µl</td>
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<td>556</td>
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<td>500</td>
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<td>E-AET %</td>
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<td>63</td>
<td>58</td>
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<tr>
<td>E-active %</td>
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<td>32</td>
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<td>32</td>
</tr>
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<td>Suppression, Con-1 %</td>
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<tr>
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</table>

For technical details, see Patients and Methods.
bestatin (Table I). The fall in suppressor cell activity during bestatin therapy, when the low Con A concentration was used for induction, was not statistically significant. But the low values for suppression are below the normal range.

DISCUSSION

Many studies have shown that patients with atopic dermatitis have a reduced immune reactivity together with an increased concentration of IgE in serum (5-8). The immunomodulating properties of bestatin (1-4) indicate that this drug possibly could correct some of the immune changes and thereby eventually improve the patients condition.

Our present study demonstrates that bestatin, 20 mg x 2 daily, does not change either the clinical course of the disease or the immune reactivity in adult patients with severe atopic dermatitis. We observed that all patients had increased IgE and circulating eosinophils in blood. The T cell percentage was within normal limits although one or two had a percentage of T cells in the lower end of the normal range. A reduction of non-specific suppressor cell activity has previously been found, but this deficiency is quantitative and is corrected by the use of a larger concentration of Con A for induction of suppressor cell activity (7) as also seen in the present investigation.

We can conclude that bestatin seems to be without value in the therapy of adult patients with severe atopic dermatitis. Whether it may be of benefit in children with moderate atopic dermatitis is unknown.

ACKNOWLEDGEMENTS

This investigation has received financial support from "Danmarks Asthma-Allergiforbund". We thank Mrs Anni Jespersen and Mrs Jette Schjødt for their excellent technical assistance.
REFERENCES

Pyoderma gangrenosum Treated with Clofazimine:
Clinical Evaluation of 7 Cases

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Seven patients with pyoderma gangrenosum have been treated with clofazimine. In contrast to the beneficial effect described in other articles only one healed. (Received March 27, 1983.)

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Clofazimine (Lamprene®) is a substituted iminophenazine dye widely used as an antileprosy drug. Several investigations have been published concerning the clinical effect of clofazimine in the treatment of pyoderma gangrenosum (1, 2, 3, 4). Most of these studies present rather convincing results with respect to healing of the ulcers.

MATERIAL AND METHODS

During 1978-82 7 patients with pyoderma gangrenosum and a duration of the disease for 2-36 months were treated with 2-300 mg clofazimine daily for 2-16 months. The patients were between 30 and 87 years old, 4 females and 3 males. This study is a retrospective clinical evaluation.

RESULTS

The results are presented in Table I. In patient 3 a regression of symptoms and clinical signs occurred during treatment with clofazimine. In the other 6 patients the effect of treatment was disappointing. In the present study we found that two patients with