# Management of Severe Atopic Dermatitis with Thymostimulin

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**Abstract**

Two patients with severe atopic dermatitis unresponsive to conventional therapy were enrolled in a clinical trial on thymostimulin (TP-1). TP-1 was administered by subcutaneous injection 1 mg/kg/day for 14 days and then 1 mg/kg/day on alternate days for 2 months. Clinical and immunological status were evaluated at baseline and at regular intervals during the treatment. Clinical severity scores included eight skin conditions (erythema, edema, vesicle, crust, excoriation, scaling, lichenification, pigmentation), two subjective components (itchiness and loss of sleep), and extent of area affected. There was a statistically significant improvement in the overall assessment of the severity scores. There were no definite changes in immunological parameters including $CD_4$, $CD_8$ T-cell subpopulations and serum IgE, but eosinophil count showed a mark decrease in one case. No serious side effects were observed.

**Key word** : Atopic Dermatitis, Thymostimulin

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**J Med Assoc Thai 2002; 85 (Suppl 2): S749-S754**

Atopic dermatitis (AD) is a common inflammatory skin condition in infants and children. Although the pathogenesis of AD is largely unknown, a number of immunologic abnormalities, including elevated and sustained serum IgE level, increased interleukin 4 production, decreased interferon gamma and impaired T-cell function have been described(1-3).

Conventional managements of atopic dermatitis include avoidance of allergens, antihistamine, and frequent applications of emollients and topical corticosteroids. Long-term use of potent topical corticosteroids and systemic corticosteroids results in significant side effects. Any treatment that could potentially reduce long-term steroid use and the associated side effects would be beneficial. In severe

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recalcitrant cases of AD, many clinical trials on new therapies focusing on possible immunological abnormalities involved in the pathogenesis have been tried. These immunomodulation therapies are Chinese herbal medicinal plants[4], cyclosporin-A [5], photochemotherapy, gamma interferon, interleukin-2, tacrolimus, ascomycin, and thymic hormones[6-10]. Thymostimulin (TP-1) which is a bovine thymic extract demonstrated the ability to regulate systemic immune abnormality by increased active T-cells, B-cells, and T-cell subsets both *in vitro* and *in vivo*. The interleukin-2 and γ-interferon production, cytotoxicity, and lymphoproliferation were significantly increased after TP-1 treatment[11-14].

A double-blind placebo-controlled studies of TP-1, and thymopoietin for the treatment of AD showed statistically significant difference in the total clinical severity scores[3,15,16]. This report was to study the efficacy of TP-1 in the management of severe atopic dermatitis. TP-1 was tried on two patients with severe recalcitrant disease.

## PATIENTS AND METHOD

Two patients diagnosed as having AD by using diagnostic criteria according to Hanifin and Rajka were recruited into the trial[17]. Case 1 was a 15-year-old girl and case 2 was a 9-year-old boy who had suffered from AD since 2 and 4 months of age, respectively. Their dermatitis was severe and resisted conventional therapy. The patients had not been treated with any immunomodulator within 60 days preceding entry into the study and they did not have significant abnormal blood chemistry. TP-1 was administered subcutaneously at a dose of 1 mg/kg/day for the first 2 weeks and then followed by 1 mg/kg/every other day for the subsequent 6 weeks. Skin test was performed on the patient prior to the start of the first injection. Intradermally TP-1 0.1 ml was injected on the anterior forearm of the patient and the presence of wheal and flare were read at 10 and 30 minutes. In addition to TP-1, the patients were instructed to continue low potency topical corticosteroids. They were hospitalized for 3 days to observe the acute adverse effect of the therapy.

The patients were assessed before entry into the study and then follow-up at day 15 (the end of daily dose), day 60 (the end of the therapy), day 180 (6 months after commencement of the therapy). Clinical severity score was evaluated and a blood sample was taken at each visit to measure complete blood count, eosinophil count, lymphocyte subset ($CD_4$ and $CD_8$), serum IgE level, renal function (BUN, creatinine) and liver function tests (bilirubin, ALT, AST, alkaline phosphatase, protein).

The clinical severity score was based on a multi-parameter scheme comprised of subjective components assessed by the patients, objective score and body surface area affected assessed by two pediatric dermatologists. Each of the individual skin signs (erythema, edema, vesicle, crust, excoriation, scaling, lichenification, pigmentation) and subjective components (itchiness and sleep loss) was graded on the scale of 0 to 7. The sum of eight skin signs and two subjective components comprised seventy per cent of the score. The remaining 30 per cent was derived from the body surface area affected. The amount of topical corticosteroids used was ascertained. Throughout the trial, all adverse experiences, cutaneous infection, and complications were recorded.

The clinical trial protocol of the study was approved by the Ethics Review Committee on Research Involving Human Subjects of the Faculty of Medicine, Siriraj Hospital, Mahidol University. All the patients and parents were fully informed and gave their informed consents to participate in the trial. Data were analyzed for statistical significance using paired-sample *t* test.

## RESULT

The changes in total clinical severity score with time and eosinophil count are shown in Fig 1 and Fig 2. Clinical scores on day15 of both cases were statistically significantly decreased from baseline ($p < 0.02$). Clinical improvement in case 1 tended to be maintained for up to day180 of the follow-up period but the disease in case 2 flared up on day 60 and subsided a few days later. Eosinophil count of case 1 was high (2,930 cell/$mm^3$) at baseline and was markedly decreased after day 5 of TP-1 therapy. There was a transient increase in the eosinophil count in case 2 after the treatment but the number decreased at day 180.

Immunological parameters and the amount of topical corticosteroids used are shown in Table 1. There were no definite changes of $CD_4$, $CD_8$ T-cell subpopulations, and serum IgE level in both cases during the treatment ($p > 0.05$). The amount of topical corticosteroid used decreased in both cases corresponding with the clinical scores.

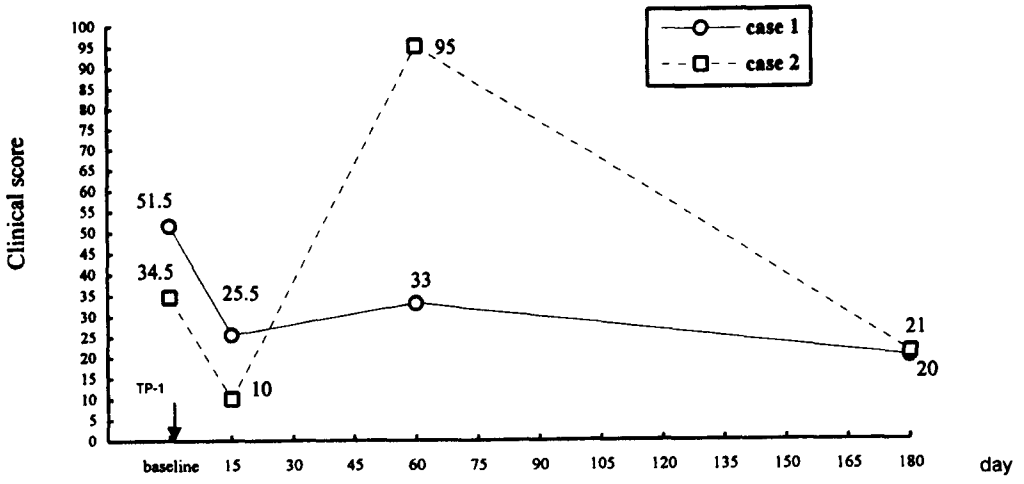


Fig. 1. Clinical severity scores.

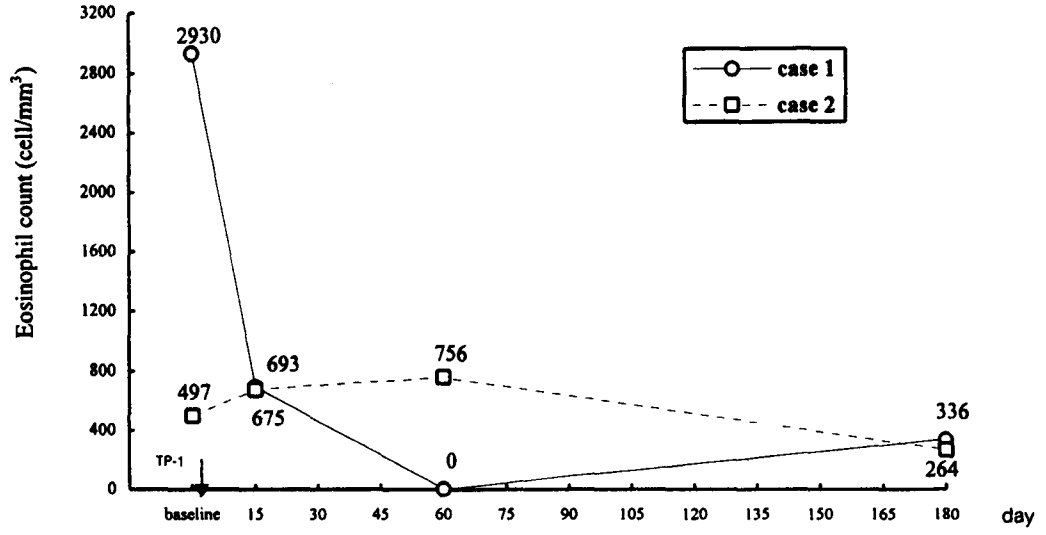


Fig. 2. Eosinophil count.

There was no change in renal and liver function tests. The result of the intradermal skin test showed no reaction and no allergic reaction was observed during the course of injections. The adverse effects detected were transient swelling and pain at the first few injection sites but lessened later in the trial. There was no cutaneous infection during the treatment.

**Table 1. Immunological parameters and steroid used.**

| | Day | $CD_4$ (cell/mm$^3$) | $CD_8$ (cell/mm$^3$) | Serum IgE (IU/ml) | Corticosteroid used (g/week) |
|---|---|---|---|---|---|
| Case 1 | 1 | 755.00 | 719.00 | $10.75 \times 10^3$ | 75.00 |
| | 15 | 730.00 | 715.00 | $7.75 \times 10^3$ | 45.00 |
| | 60 | 483.00 | 558.00 | $10.75 \times 10^3$ | 18.75 |
| | 180 | 891.00 | 939.00 | $4.10 \times 10^3$ | 10.00 |
| Case 2 | 1 | 1,677.00 | 1,591.00 | $26.00 \times 10^3$ | 30.00 |
| | 15 | 1,035.00 | 1,018.00 | $7.75 \times 10^3$ | 15.00 |
| | 60 | 1,374.00 | 1,063.00 | $10.75 \times 10^3$ | 5.00 |
| | 180 | 1,180.00 | 1,087.00 | $9.25 \times 10^3$ | 3.00 |

## DISCUSSION

Thymic hormone extract in the treatment of AD aims to repair the deficit in the cellular immunity found in these patients. AD patients with major defects in type IV cell-mediated immunity respond well to TP-1 therapy. Poor treatment response is found in those with major defects in B-cell humoral immunity and IgE mediated hypersensitivity. TP-1 reduces the clinical symptoms and the extent of body involvement in patients with severe recalcitrant disease. With the treatment, clinical features including erythema, oozing and discharge improve quickly (16). Therapy with TP-1 and topical corticosteroids is effective only in the acute exacerbation stage. The effect of TP-1 on chronic lichenoid type lesion is disappointing, so long-term therapy is not recommended. TP-1 may be useful as monotherapy or as an adjunct to conventional therapy in the treatment of patients with severe AD(15,16).

The disadvantage of TP-1 is its expensive price and the course of injections is quite long. Patient who will be highly recommended to participate in this kind of therapy which comprises of many subcutaneously injections should be patients who suffer from the most severe form of AD and not responsive to conventional therapy. As TP-1 is non-human peptide, it may cause severe anaphylaxis, thus it is important to check for any allergic reactions (18). In this trial, there was no serious significant side effect observed and it was well tolerated.

There was a statistically significant improvement in the clinical score of the TP-1 treated patients in this study but there was no correlation between clinical outcome and immunologic parameters. Like a previous study, T-cell subpopulations and serum IgE level demonstrated no definite changes(15). It should be noted that improvement during the course of treatment may also occur from topical corticosteroid and emollient therapy. This report suggests that TP-1 may have a beneficial effect in severe widespread recalcitrant AD, however, the authors could not definitely conclude the data because only two cases were studied. Further study including a large number of patients and a control group is needed to confirm the beneficial effect of TP-1.

## ACKNOWLEDGEMENTS

The authors wish to thank Serono Singapore Pte Ltd. and Pacific Healthcare (Thailand) who sponsored TP-1. We also thank Dr. Lim Khye Sing, the clinical research manager of Serono, Singapore, who gave excellent consultation of the study.

(Received for publication on February 1, 2002)

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# การศึกษาทดลองรักษาโรคผื่นภูมิแพ้ผิวหนังด้วยสารธัยโมสติมูลิน

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การศึกษานี้เป็นการทดลองใช้สารธัยโมสติมูลินรักษาผู้ป่วยโรคผื่นภูมิแพ้ผิวหนัง 2 รายที่มีอาการรุนแรงมาก และไม่ตอบสนองต่อการรักษาด้วยวิธีปกติ วิธีการรักษาทำโดยฉีดสาร thymostimulin ขนาด 1 มก/กก/วันเข้าใต้ชั้นผิวหนัง เป็นเวลา 2 สัปดาห์ หลังจากนั้นใช้ขนาด 1 มก/กก วันเว้นวัน ฉีดต่ออีก 6 สัปดาห์ ก่อนและระหว่างการรักษาผู้ป่วยจะได้รับการตรวจร่างกายเพื่อประเมินความรุนแรงของโรคอย่างละเอียดและเจาะเลือดเป็นระยะ แพทย์จะตรวจระบบผิวหนังดูความแดง ความบวม ตุ่มน้ำ คราบสะเก็ด รอยเกา การเปลี่ยนแปลงของสีผิวและคำนวณพื้นที่ผิวบริเวณที่เป็นผื่น ผู้ป่วยมีส่วนร่วมในการประเมินอาการคันและการอดนอน ตรวจระบบภูมิคุ้มกันจากเลือดโดยดูจำนวนเม็ดเลือดขาวอีโอสิโนฟิล ระดับอิมมูโนโกลบูลินชนิดอี จำนวน $CD_4$ และ $CD_8$ ผลการรักษาพบว่าระดับความรุนแรงของโรคลดลงชัดเจนแต่ไม่พบความเปลี่ยนแปลงทางระบบภูมิคุ้มกันของร่างกายในผลเลือดและไม่พบผลข้างเคียงที่อันตรายจากการใช้สาร thymostimulin

**คำสำคัญ** : โรคผื่นภูมิแพ้ผิวหนัง, สารธัยโมสติมูลิน

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