Clinical Study of Cyclosporin A for Psoriasis in China

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Background: The efficacy of Cyclosporin A (CyA) in the treatment of psoriasis is well recognized, the dosage less than 5mg/kg per day (mg/kg/d) is recommended.

Objective: The purpose of this study is to evaluate the indication, dose, course and side-effects of CyA therapy for psoriasis, especially in China.

Methods: Forty patients with psoriasis were treated with doses of CyA 5mg/kg/d, compared with 20 patients treated with Tigason 1mg/kg/d by Global PASI.

Results: 1. Of 40 patients 33 patients (82.5%) were cured clinically in 4-5 weeks and all the patients (100%) had responses to the therapy.
2. The efficacy and the Global PASI reduction of CyA therapy were significantly better than that of Tigason therapy.
3. During the CyA therapy, no severe side-effects and obvious laboratory changes were found.

Conclusion: CyA (5mg/kg/d) was satisfactory for psoriasis, especially for psoriasis pustulosa, arthropathica and erythroderma. CyA was found to be superior to Tigason. The therapy course and side-effects seemed to be related to the dosage. (Ann Dermatol 7(4):313-317, 1995)

Key Words: Cyclosporin A, Psoriasis

As a selective immunosuppressant mainly for cell-mediated immunity, CyA has been used from organ transplantation to immunodiseases, dermatosis including psoriasis and has significant efficacy1,2. Other than psoriasis, sufficient knowledge or information about indication, dose of therapy, course and side-effects are not known especially in China. Forty patients with psoriasis have been treated with CyA. The patients are observed systemically and compared with the Tigason treated group.

MATERIAL AND METHODS

Case selection and therapy method

1. CyA group: From 40 cases of psoriasis treated with CyA 31 cases were treated in hospital, with the mean age of 39.0 and the disease course of mean 9.4 years. There were 22 cases of psoriasis vulgaris (16 cases in progress), 2 cases of pustulosa of the palms and soles, one erythroderma case, 2 cases of generalized pustulosa, 3 arthropathica cases, one case of guttata; 9 cases were treated in clinic, with the mean age of 40.9 and the disease course of mean 15.0 years. These include 8 cases of vulgaris (6 cases in progress), and one erythroderma case.

The initial dose is 5mg/kg/d. Drug dose is reduced when the patients have been clinically cured sufficiently in 3-4 weeks. The patients continued the therapy at a minimum dose for 6-8 weeks. A few of the patients received an initial dose 2-4mg/kg/d and were slowly responsive, the dosage of drug was gradually increased to about 5mg/kg/d. The patients treated in clinic were followed weekly.

2. Tigason group: All of 20 cases were treated in hospital with the mean age of 40.7, and disease course of mean 9.2 years. There are 15 cases of vulgaris (12 cases in progress), 2 cases pustulosa of the palms and soles, one erythroderma case, and one case each of generalized pustulosa and arthropathica.

The initial dose is 1mg/kg/d. Drug dose is reduced when the patients have been clinically

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cured or showed obvious efficacy in 4-5 weeks and therapy is continued for 6-8 weeks.

Assessment criteria.\textsuperscript{1-7}

1. Criteria of efficacy, Clinical cure: thorough disappearance of erythema, scale and itchness or remains of only slight infiltration and pigment. Significant efficacy: obvious subsidence of erythema, scale and itchness 50\% or more reduction of area of skin lesion.

Failure: no obvious changes of eruption and less than 50\% reduction of skin lesion.

2. Global Psoriasis Area and Severity index assessment of CyA and Tigason therapies: According to the degree of erythema, scale, itchness and percentage of affected area, the Global PASI score is estimated before and during the therapies. The area affected is more than 70\% and the degree of the lesions and symptoms are severe(=6). Affected area of 69-50\% and moderate degree(=5). Affected area of 49-30\% and moderate degree(=4). Area 29-10\% and degrees moderate to slight(=3). Area 9-2\% and slight degree(=2). Only slight infiltration or pigment(=1). The lesions and symptoms disappeared totally(=0).

3. Side-effects: The symptoms and dosage of CyA therapy are recorded. Blood pressure is measured on daily basis.

4. Laboratory changes: Before and during CyA therapy, liver function, renal function, blood, urine and stool routins tests and immunologic index are examined and the blood level of CyA is detected.

RESULT

CyA efficacy: 3-7 days after CyA treatment, itchting begins to be relieved, erythema turns lighter in color and the scale reduces. In 3-4 weeks after CyA therapy, itchness, erythema, or scales might disappear, leaving only a few pigments and a slight infiltration. In psoriasis pustulosa of the palms & soles, pustules and vesicles are usually absorbed in 7 days and desquamation appears; the skin lesions disappear significantly and are cured in 4-5 weeks. In 2 cases of psoriasis erythema and 2 cases of psoriasis with generalized pustulosa, erythema subsides dramatically in about 10 days and pustules absorb; the skin lesions disappear furthermore and are cured in 4-5 weeks. All of 4 patients had misused large doses of corticosteroid therapy for a considerable long period of time which resulted in a more severe lesion. During CyA therapy, corticosteroid can be reduced successfully and removed completely or maintained at 5mg/d. In psoriasis arthropathica, articular swelling and pain subside in 10-14 days, whereas skin lesions disappear at an earlier stage.

Comparison: In 40 cases receiving CyA therapy, 33 cases are clinically cured (cure rate 82.5\%); all of 40 cases are responsive to the therapy(efcacy rate 100\%). CyA therapy seems to be superior to Tigrason.

Observed by Global PASI in hospitalized patients', 31 cases treated with CyA and 20 cases with Tigrason, both groups begin to show effect at the first week of therapy. In CyA group, after 3-4 weeks lesions improved and finally reached clinical cure level. In Tigrason group some patient's erythema and infiltration would not change or subside very slowly, so the efficacy is not complete.

CyA therapy usually start to show effect in 3-7 days(5.4 \pm 3.2) but Tigrason treated group in 5-10 days(6.9 \pm 3.5). CyA therapy course in hospital is 28.5 \pm 7.5 days but Tigrason is hospitalized for 34.2 \pm 10.6 days. There is a difference of about one week.

Detection of CyA blood level: Eighteen samples in 15 cases are detected by polarized fluorescent immunoassay. Samples of its valley value are taken at morning before taking drug and top value in 4 hours after drug intake. The dosage of CyA in these patients is about 5mg/kg/d after 14 days therapy. Valley value of CyA blood level is mean 111.73 \pm 120.11ng/ml, top value 281.15 \pm 274.36ng/ml.

Side-effects: When CyA dose is 2-3mg/kg/d,

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Cure</th>
<th>Significant efficacy</th>
<th>Failure</th>
<th>Cure % rate</th>
<th>Efficacy % rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyA</td>
<td>40</td>
<td>33</td>
<td>7</td>
<td>0</td>
<td>82.50</td>
<td>100.00</td>
</tr>
<tr>
<td>Tigason</td>
<td>20</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td>30.00</td>
<td>85.00</td>
</tr>
</tbody>
</table>
there seems to be no side-effects. But in 5mg/kg/d, side-effects seem to appear. Gastrointestinal reactions appear early and are the most common symptoms. These include appetite, anorexia, abdominal discomfort and diarrhea. Patients often complain of fatigue as well. Urinary tract stimulative symptoms include urinary frequency and dysuria. Hypertension usually appears from 7-10 days to the end of CyA therapy. Blood pressure is all less than 21/13 KPa and can be controlled by antihypertensives. Continuing the therapy, there shows no tendency of blood pressure rise. Other side-effects are paresthesia, tremor, arthralgia and hypertrichosis. Only one of the patients had folliculitis in his lower legs and is cured by antibiotic cream. Side-effects are so slight that it might not affect CyA therapy. Continuing the use of CyA therapy, it would not turn severe and almost all of patients maystand it gradually or symptoms would disappear.

Laboratory changes: Four cases(mean dose 5.28mg/kg/d) has SGPT rising but only one reaches 192u and the others are between 40-80u. Continuing to use the therapy and liver-protect drug, there is no rising tendency.

As CyA therapy is reduced and eventually discontinued, SGPT level return normal. Bilirubin level rose to 1.68mg/ml in one case. Three cases had a slight rise in BUN in renal function but the values were all less than 100mg/dl. In 2 cases of CyA therapy, WBC were reduced to 3.3 and 3.6 × 10^9/L respectively at the start of therapy. As the treatment continues, WBC rose to 6.0−8.0 × 10^9/L. Three cases had a reduction of Lymphocyte transformation test and Erythrocyte rosette forming.

**Table 2. Side-effects of 40 cases with psoriasis by CyA therapy**

<table>
<thead>
<tr>
<th>Case</th>
<th>Mean dose(mg/kg/d)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast pain</td>
<td>1</td>
<td>6.35</td>
</tr>
<tr>
<td>Browsiness</td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>1</td>
<td>6.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>5.15</td>
</tr>
<tr>
<td>Tinitus</td>
<td>2</td>
<td>5.48</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>Urinary tract stimulation</td>
<td>9</td>
<td>5.07</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>4.95</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>4.81</td>
</tr>
<tr>
<td>Paraeesthesia</td>
<td>4</td>
<td>4.97</td>
</tr>
<tr>
<td>Gastrointestinal reaction</td>
<td>12</td>
<td>5.01</td>
</tr>
</tbody>
</table>
cell. Two cases have a reduction of complement CH50. However there are not any changes in complement C3, immunoglobulin, 2 microglobin, platelet, and hemoglobin.

**Recurrence after CyA therapy:**

1. During CyA therapy, 3 cases had new eruptions. In these cases CyA doses were all less than 3mg/kg/d. After adding about 5mg/kg/d and applying steroid cream, the eruption subsided.

2. In reducing the CyA dosage, 4 cases had recurring skin lesions. In these cases dosage was quickly reduced from 4-5.7mg/kg/d to 2-4.73 mg/kg/d respectively. However, the skin lesions disappeared soon after applying steroid cream.

3. After stopping the CyA therapy, one case recurred in 2 weeks, in one month there were 2 recurrences, 2 in 2 months, one in 6 months, but 6 cases did not recur after even months. Taking 1-2mg/kg/d CyA in recurring cases, their skin lesions soon subsided again. The severity of psoriasis in these patients is slight lesser than before therapy and the skin lesions were able to be controlled by Chinese herbs or steroid cream. After following one year, the recurrence rate of CyA therapy is about 50%.

**DISCUSSION**

Since the first report by Muller in 1979 that CyA is effective in psoriasis, many studies were done overseas, however none in China. In our study of CyA initial dose is 5mg/kg/d for treating psoriasis. It begins to show effect in 3-7 days and most of the cases have reached clinical cure and had satisfactory efficacy in 3-4 weeks. Then the dose is gradually reduced and the therapy end in 2-3 months. The initial dose of 5mg/kg/d might shorten the therapy course in hospital and show efficacy quickly. Further lowering the dose would maintain efficacy and prevent recurrence.

If the dose of CyA is lower than 5mg/kg/d, it will postpone the effect of appearance and clinical cure. So we suggest that the initial dose of 5mg/kg/d is suitable and be continued for about 4 weeks. When clinical cure is satisfactory, the dose will be reduced and maintained at a lower dosage. Detection of valley and top CyA blood level might prevent severe side-effects, especially for liver and kidney toxicities. Our study shows that CyA efficacy is dramatic, with its clinical cure rate of 82.5% and efficacy rate of 100%. CyA is obviously superior to Tigason. It has satisfactory effect on psoriasis pustulosa, erythroderma and arthropathica, especially for patients having psoriasis worsen and generalized due to the misuse of corticosteroid therapy. CyA therapy may reduce the dosage of steroid and stop steroid therapy completely. However, Tigason have some shortcomings. Therefore, it is recommended that CyA is used for severe and stubborn psoriasis.

There are not many severe side-effects in our study of low dose CyA therapy. Gastrointestinal reaction is common, can be relieved by taking drug after food intake. Other side-effects such as frequent micturition, tremor and so on can be relieved or disappeared when continuing therapy. Hypertension can be controlled by antihypertensives and will not affect the therapy. During CyA therapy, there are no obvious laboratory changes including liver and renal function; blood, urine, stool routine examination and immunoidex. However before and during CyA therapy, detection of liver and renal function is essential. It is important to be cautious with cases of liver or renal dysfunction.

During CyA therapy, recurrence of eruption always can be seen in CyA dosage of less than 3mg/kg/d. It shows that initial dose of CyA can not be too low nor be reduced too quickly. It is suggested that the CyA therapy might be similar to the usage of steroids. The initial dose will be suitable and reduced gradually to prevent recurrence and relapse. After stoping CyA therapy, most of the recurrence happen in 1-2 months. It shows that the drug can not be stopped all too early. The lowest dosage(0.5-1mg/kg/d)should be maintained for at least 3-6 months.

**Acknowledgment**

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**REFERENCES**