Cyclosporin A Therapy of Immune-Mediated Thrombocytopenia in Children

To the Editor:

Immune thrombocytopenic purpura (ITP) of childhood is usually a self-limited disorder with spontaneous and complete recovery in 80% to 90% of cases. In the remaining cases, the course is chronic. Splenectomy resolves thrombocytopenia in 70% to 75% of chronic cases, but in a small group of cases (5% of all cases), the thrombocytopenia becomes refractory to therapeutic intervention including steroid therapy, intravenous Ig, Rh(D) immune globulin and immunosuppressive chemotherapeutic agents. Thus, new therapeutic modalities are needed for these refractory ITP cases.

ITP appears to be secondary to platelet reactive antibodies produced by B cells. More recently, platelet reactive T cells have been identified and probably supply "help" to platelet-reactive B cells. Cyclosporin A (CsA) has the ability to inhibit T-cell and T-cell-dependent B-cell function. In addition, it has been reported to be successful in treatment of adults with refractory chronic ITP. Moreover, because it has been suggested that ITP is primarily caused by a T-cell defect rather than a B-cell defect, specific suppression of T-cell suppression may be efficacious. The efficacy of CsA in children with chronic ITP has not been studied. We evaluated the ability of CsA to increase platelet counts in children with refractory ITP in a prospective pilot study. Children ≤15 years of age were eligible if they had ITP dependent

Table 1. Characteristics of ITP Patients Treated With Cyclosporin A (CsA)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)/Sex</th>
<th>Duration before CsA (mo)</th>
<th>Previous Therapy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVIG</td>
<td>Prednisone</td>
</tr>
<tr>
<td>1</td>
<td>13/M</td>
<td>3</td>
<td>1 g/kg × 1</td>
<td>2 mg/kg × 3 mo</td>
</tr>
<tr>
<td>2</td>
<td>14/M</td>
<td>3</td>
<td>No</td>
<td>1.5 mg/kg × 3 mo</td>
</tr>
<tr>
<td>3</td>
<td>3/M</td>
<td>10</td>
<td>1 g/kg × 2</td>
<td>4 mg/kg × 3 mo</td>
</tr>
<tr>
<td>4</td>
<td>5/F</td>
<td>3</td>
<td>1 g/kg × 1</td>
<td>1 mg/kg × 3 mo</td>
</tr>
<tr>
<td>5</td>
<td>11/M</td>
<td>6</td>
<td>500 mg/kg × 5d</td>
<td>20 mg/kg/d × 5d</td>
</tr>
</tbody>
</table>

Abbreviations: IVIG, intravenous Ig; Anti-D, Rh(D) immune globulin; ANA, antinuclear antibody; DAT, direct antiglobulin test; –, negative; +, positive.
We enrolled five children with chronic ITP. Ages ranged from 3 to 14 years with a median of 11 years. Ratio of male to female was 4:1 (Table 1). All children had been previously treated with prednisone and four of five had also proven refractory to intravenous Ig, Rh(D) immune globulin (WinRho; Rh Pharmaceuticals, Winnipeg, Canada) was tried in two children with no response before entry on study. One child had concurrent warm antibody autoimmune hemolytic anemia. All patients had a starting platelet count \( \geq 40 \times 10^9/L \).

Evaluation for response to CsA therapy showed that one patient had an increase in platelet count \( \geq 25 \text{cell} \times 10^9 \text{cells}/L \) at 5 mg/kg/d and three additional patients at 10 mg/kg/d (Fig 1, A and B). Only two had an increase in platelet count of \( \geq 50 \times 10^9 \text{cells}/L \) and none had an increase of \( \geq 100 \times 10^9 \text{cells}/L \) (Fig 1B). Whole blood cyclosporine levels \( \geq 150 \mu g/L \) were attained in all patients. Length of any response (platelets \( \geq 25 \times 10^9 \text{cells}/L \)) was 1 week in two patients, 2 weeks in one, and 4 weeks in one. All responses were transient with the longest response lasting 4 weeks. Platelet counts declined in four children while on CsA.

Toxicity observed in children while on cyclosporine was headache,\(^4\) gastrointestinal upset/decreased appetite,\(^2\) irritability,\(^2\) chest pain,\(^1\) peripheral neuritis,\(^1\) and hypertension.\(^2\) Although all patients were on prednisone before entering study, all of these symptoms began after starting CsA. None of the patients had evidence of renal dysfunction (creatinine \( \geq 2 \times \) baseline) and/or liver dysfunction (ALT or AST \( \leq 150 \)).

Despite the wide variation in CsA levels during therapy and small numbers of children studied, the data suggested a relationship between the CsA levels and increase in platelets counts (Fig 2; \( R = .72 \)). On the other hand, relatively high levels of CsA (\( \geq 500 \mu g/L \)) were required to obtain increases of \( \geq 50 \times 10^9/L \) over baseline.

In summary, we prospectively evaluated the efficacy of T-cell-directed therapy using CsA in children with chronic ITP. Although a small number of children were evaluated, we saw a consistent

![Fig 1. Platelet counts after Cyclosporin A therapy. Platelet counts were measured weekly after administration of CsA. (A). Three patients (patients 3 through 5) were given 5 mg/kg/d and monitored for a response (platelet level increase of \( \geq 25,000 \times 10^9/L \)). One patient responded and was treated for \( >2 \) weeks. (B). All patients who failed the lower dose and two other patients (1 and 2) were given 10 mg/kg/d. One patient received CsA both before and after splenectomy.](https://example.com/fig1)

![Fig 2. Correlation of Cyclosporin A levels and change in platelet counts. Trough whole blood levels of Cyclosporin A using a monoclonal assay for the active metabolite was done with each platelet count. This figure shows the change in platelet count (\( \Delta \) platelet count) over baseline in comparison with the CsA level done at the same time. A simple correlation was performed and the formula for best fit is shown.](https://example.com/fig2)
response pattern in four of five children. However, the response was minimal and transient. Although not life threatening, toxicity associated with CsA treatment appeared to be greater than that seen in other children receiving CsA for other indications with similar blood levels. The trend toward a direct correlation of whole blood CsA levels and platelet responsiveness implies that relatively high blood levels of CsA (≥500 µg/L) are necessary to attain a platelet increase of ≥50 × 10^9/L. Attainment of high CsA levels in these children appeared to result in intolerable toxicity for some. These results suggest that CsA, as given in this trial, is not an effective therapy of chronic ITP in children. Shorter high-dose regimens may provide a better response in future studies.

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REFERENCES
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