Intravenous infusion of gammaglobulin (IVGG) has been extensively used in the treatment of immune thrombocytopenic purpura (ITP) in adults to acutely raise the platelet count but not as a maintenance therapy. This report describes the maintenance treatment of adults with chronic ITP using repeated infusions of 800 to 1,000 mg/kg of IVGG. Sixteen of 40 patients were able to discontinue all therapy after receiving between one and 15 infusions. Five patients achieved remission and 11 other patients became stable without therapy (SWT) maintaining a platelet count >20,000/μL without bleeding. The average quantity of gammaglobulin received for all patients was 606 g per patient. Of the 30 patients who underwent but did not respond to splenectomy, 11 (37%) were able to discontinue all therapy by either achieving remission (5) or becoming SWT (6). None of the five patients who achieved remission did so after only the initial therapy; all first received between one and 12 maintenance infusions. The ten splenectomized patients who were unresponsive to IVGG also failed to subsequently respond to conventional therapy including immunosuppressive agents and androgens. No toxicity of IVGG was seen except for postinfusion headaches. IVGG is an effective although expensive maintenance therapy for adults with ITP and is useful in patients who have not responded to splenectomy.

IMMUNE THROMBOCYTOPENIC purpura (ITP) is a hemorrhagic disorder characterized by low platelet counts, normal or increased numbers of bone marrow megakaryocytes, and the absence of other causes of increased platelet destruction. Platelet destruction in ITP is rapid presumably by temporarily interfering with mononuclear phagocyte system Fc receptor function. Initial enthusiasm for this therapy, however, was tempered by the observation that the platelet count returned rapidly to the pretreatment range in most patients. IVGG has not usually been considered to be feasible as a maintenance treatment because most adult patients have little apparent response of their platelet counts to a single infusion of 400 mg/kg (one day's dose), and therefore it has been thought that the entire five-day course of treatment would have to be repeated.

The aim of this study was to define the potential clinical usefulness of single dose (800 to 1,000 mg/kg) infusions of IVGG in the long-term management of adults with chronic ITP, especially in patients unresponsive to splenectomy. In particular, we wished to determine the percentage of such patients who could be maintained in this fashion and who would eventually achieve an adequate platelet count (>20,000/μL) without further therapy.

MATERIALS AND METHODS

Patients. From 1982 to 1985, 40 consecutive adults with chronic ITP who received IVGG at The New York Hospital/Cornell Medical Center and who met the following criteria were included in this study: (1) ITP diagnosed >6 months before initial IVGG infusion; (2) splenectomy if performed (30 of 40) >3 months before initial IVGG infusion; and (3) IVGG treatment initiated for long-term management of the low platelet count (not as preparation for surgery). Patients had an average duration of disease of 4.5 years; 28 were females and 12 males. The mean age was 48.3 years (range, 20 to 80). Thirty of the 40 patients had had splenectomy an average of 3 years before IVGG treatment and all patients had received other therapy of their ITP before beginning IVGG (Table 1). The protocol of study was approved by the Institutional Review Board of The New York Hospital and consent was obtained from the patients when they were enrolled.

Gammaglobulin treatment. Thirty-two patients were infused with the pH 4.0 IVGG preparation (Sandoglobulin; Swiss Red Cross, Berne, Switzerland), three patients received a polyethylene-glycol preparation (Endoglobulin; Immuno AG, Vienna, Austria), two patients received a different polyethylene glycol preparation (Veinoglobin; Alpha Therapeutics, Los Angeles) and three patients received a chromatographically treated preparation (Gammagard; Hyland Therapeutics, Glendale, CA). As initial therapy, 5% to 6% gammaglobulin in isotonic saline solution, at a total dose of 2 g/kg body weight, was administered in equal doses over two to five days by IV infusion. Maintenance infusions of 60 g were administered whenever platelet counts fell below 20,000/μL. IVGG treatment was initiated at platelet counts >20,000/μL only in patients whose platelet counts were being sustained by corticosteroids. The dose of the first maintenance infusion was usually 0.5 g/kg but this was increased to 800 to 1,000 mg/kg in subsequent infusions to maximize the therapeutic effect and to minimize the frequency of infusions. The infusion rate was approximately 250 mL/h. Other medications (usually corticosteroids) were discontinued 1 to 3 weeks after initial IVGG treatment; however, several patients who did not respond adequately to IVGG alone later received alternate day corticosteroid therapy in conjunction with IVGG. They are in the

From the Department of Pediatrics and Medicine, The New York Hospital/Cornell Medical Center, and The Mount Sinai Medical Center.

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Address reprint requests to J.B. Bussel, MD, New York Hospital-Cornell Medical Center, 525 E 68th St, Room N-740, New York, NY 10021.

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Table 1. Clinical Information on Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>No. of IVGG Infusions</th>
<th>Duration of Disease Before IVGG</th>
<th>Prior Therapy</th>
<th>Therapy at IVGG</th>
<th>Pre-IVGG Platelet Count</th>
<th>Peak Platelet Count</th>
<th>IVGG</th>
<th>Outcome</th>
<th>Date of First IVGG</th>
<th>Date of Last IVGG</th>
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<tr>
<td>1</td>
<td>63/F</td>
<td>9</td>
<td>5-10 yr</td>
<td>Imuran; Prednisone</td>
<td>Solumedrol 64/d</td>
<td>7</td>
<td>38</td>
<td>540 g</td>
<td>REM$_5$</td>
<td>11/85</td>
<td>1/5/86</td>
</tr>
<tr>
<td>2</td>
<td>46/F</td>
<td>12</td>
<td>2 yr</td>
<td>danazol; cytoxan; prednisone</td>
<td>Imuran 50/d</td>
<td>35</td>
<td>277</td>
<td>1,440</td>
<td>M$_4$</td>
<td>10/85</td>
<td>8/18/86</td>
</tr>
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<td>3</td>
<td>37/F</td>
<td>10</td>
<td>5 yr</td>
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<td>Prednisone 20 mg</td>
<td>6</td>
<td>435</td>
<td>228</td>
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<td>4/85</td>
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<td>4</td>
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<td>12 yr</td>
<td>Cytoxan; Imuran; vincristine; danazol; prednisone</td>
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<td>13</td>
<td>52</td>
<td>273</td>
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<td>6/85</td>
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<td>5</td>
<td>71/F</td>
<td>15</td>
<td>5 yr</td>
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<td>10</td>
<td>65</td>
<td>657.5</td>
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<td>6/30/86</td>
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<td>6</td>
<td>73/F</td>
<td>6</td>
<td>4 yr</td>
<td>Imuran; Chlorambucil; danazol; Velban; prednisone</td>
<td>Prednisone 30 mg</td>
<td>26</td>
<td>61</td>
<td>298</td>
<td>REM$_4$</td>
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<td>5/13/86</td>
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<td>7</td>
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<td>Prednisone; danazol</td>
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<td>176</td>
<td>168</td>
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<td>12/22/87</td>
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<td>11</td>
<td>15 yr</td>
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<td>danazol 200 mg</td>
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<td>954</td>
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<td>9/85</td>
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<td>Prednisone 60 mg</td>
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<td>11</td>
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<td>2 yr</td>
<td>Prednisone; plasmapheresis; danazol</td>
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<td>56</td>
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<td>7/26/83</td>
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<tr>
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<td>53/F</td>
<td>5</td>
<td>2 yr</td>
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<td>Prednisone 60 mg</td>
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<td>340</td>
<td>160</td>
<td>REM$_5$</td>
<td>1/83</td>
<td>1/17/83</td>
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<td>13</td>
<td>80/F</td>
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<td>25 yr</td>
<td>Prednisone; vincristine</td>
<td>Prednisone 15 mg</td>
<td>4</td>
<td>33</td>
<td>582</td>
<td>SWT$_4$</td>
<td>5/82</td>
<td>7/23/84</td>
</tr>
<tr>
<td>14</td>
<td>36/F</td>
<td>8</td>
<td>4 yr</td>
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<td>Prednisone 10 mg</td>
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<td>492</td>
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<td>11/84</td>
<td>?</td>
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<td>8</td>
<td>8 yr</td>
<td>Vincristine; vinblastine-loaded platelets; liver radiation; cytoxan; steroids</td>
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<td>Gender</td>
<td>Duration</td>
<td>Treatment</td>
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<td>Date of Death</td>
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<td>17</td>
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<td>563</td>
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<td>22</td>
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<td>23</td>
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<td>600</td>
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<td>24/F</td>
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<td>546</td>
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<td>Prednisone</td>
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<tr>
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<td>None</td>
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<td>1/83</td>
<td>12/5/83</td>
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<td></td>
</tr>
<tr>
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<td>225</td>
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<td>12/21/83</td>
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<td></td>
</tr>
<tr>
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<tr>
<td>40</td>
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<td>1 yr</td>
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<td>40</td>
<td>312</td>
<td>1/84</td>
<td>6/25/84</td>
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</table>
IVGG refractory group and their subsequent course with combined IVGG/alternate day prednisone was considered separately in the Results and Discussion sections.

Clinical outcome. The clinical outcome was assessed 12 to 48 months after initial IVGG therapy and was defined as follows: Remission (REM), platelet count >150,000/μL requiring no treatment for at least 3 months; stable without therapy (SWT), platelet count >20,000/μL without any therapy for at least 3 months and without symptoms other than minimal bruising and scattered petechiae; maintenance (M), periodic single infusions of gammaglobulin without symptoms other than minimal bruising and scattered petechiae; and refractory (REF), failure to maintain a platelet count >20,000/μL despite infusion of 1 g/kg of IVGG every 2 weeks.

Analysis of data. Data were described using means, medians, and ranges. Medians were used to describe the intervals between infusions because means were distorted by the long time until the second infusion in a small number of patients. Chi-square analysis was used to compare groups of patients.

RESULTS

All patients. For the entire group of 40 patients, the average platelet count before IVGG infusion was 22,150/μL (median, 20,000/μL) and the average postinfusion peak platelet count was 197,300/μL (Table 2). Five (12.5%) achieved an unmaintained REM, and 11 (27.5%) became SWT. Thus there was a total of 40% of patients who were able to discontinue all treatment by virtue of improvement in their disease even if not all achieved remission (see Table 3 for description of the SWT patients). Thirteen (32.5%) patients continued to require M therapy and 11 (27.5%) became REF to IVGG (Tables 1 and 2). The median number of days from initial therapy to the time of the first maintenance infusion was 17 days; the median time between the first and the second maintenance infusions was 14 days. Previously splenectomized patients tended to have a greater initial response to IVGG than did nonsplenectomized patients (average postinfusion counts, 204,900/μL vs 145,300/μL); this result did not achieve statistical significance (P > .1).

Splenectomized patients. Of the 30 chronic splenectomized patients, five achieved REM, and six were SWT; a total of 11 of 30 (37%) no longer required any therapy (Table 2). Long-term outcome was related to neither the pretreatment nor the peak postinfusion platelet counts (Table 4). There was a tendency for those patients with shorter durations of disease and those >40 years of age to have a better long-term response to IVGG (Table 1).

The five patients who achieved REM had an average duration of disease of 4 years and received as few as one to as many as 12 maintenance infusions (Fig 1). At the time of evaluation, three patients had been in stable REM for >36 months and the other two had been in REM for >6 months; two of the five had had initial peak platelet responses to 2 g/kg of IVGG of only 38,000/μL and 56,000/μL (Table 1, no. 1 and 11).

The six patients who became SWT averaged 13 months since their last infusion at the time of evaluation. Their most recent platelet counts ranged between 18,000/μL (no. 4) and 98,000/μL (no. 14) (Table 3).

Of the nine patients who continued to require maintenance infusions at 2- to 4-week intervals (Fig 2), four continued to receive IVGG infusions at 2- to 5-week intervals at the time of evaluation, three received alternate day prednisone alone, one resumed corticosteroids, and one was lost to follow-up. Only three of the ten REF patients had initial platelet

Table 2. Results of Maintenance Therapy for Chronic ITP: Summary

<table>
<thead>
<tr>
<th>Chronic Patients</th>
<th>Total IVGG (g)</th>
<th>Platelet Count*</th>
<th>Outcome</th>
<th>No Longer Requiring Therapy (%)</th>
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</thead>
<tbody>
<tr>
<td>Splenectomized</td>
<td>N</td>
<td>Pre</td>
<td>Peak</td>
<td>REM</td>
</tr>
<tr>
<td>30</td>
<td>644</td>
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<td>204.9</td>
<td>5</td>
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<td>10</td>
<td>476</td>
<td>27.2</td>
<td>145.3</td>
<td>0</td>
</tr>
<tr>
<td>All patients</td>
<td>40</td>
<td>22.15</td>
<td>197.3</td>
<td>5</td>
</tr>
</tbody>
</table>

*Platelet counts x 10^3/μL.

Table 3. Platelet Counts in Patients Who Became SWT After Receiving IVGG Treatment

<table>
<thead>
<tr>
<th>SWT Patient</th>
<th>Splenectomy (Yes/No)</th>
<th>IVGG Pre-Platelet Count*</th>
<th>Platelet Count</th>
<th>Therapy at Time of Pre-Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Y</td>
<td>13</td>
<td>18</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>Y</td>
<td>4</td>
<td>43</td>
<td>Prednisone 15 mg/d</td>
</tr>
<tr>
<td>14</td>
<td>Y</td>
<td>25</td>
<td>98</td>
<td>Prednisone 20 mg/d</td>
</tr>
<tr>
<td>15</td>
<td>Y</td>
<td>3</td>
<td>21</td>
<td>Prednisone 80 mg/d</td>
</tr>
<tr>
<td>16</td>
<td>Y</td>
<td>30</td>
<td>38</td>
<td>Prednisone 40 mg/d</td>
</tr>
<tr>
<td>17</td>
<td>Y</td>
<td>47</td>
<td>27</td>
<td>Prednisone 40 mg/d</td>
</tr>
<tr>
<td>31</td>
<td>N</td>
<td>32</td>
<td>82</td>
<td>None</td>
</tr>
<tr>
<td>32</td>
<td>N</td>
<td>28</td>
<td>110</td>
<td>None</td>
</tr>
<tr>
<td>34</td>
<td>N</td>
<td>9</td>
<td>73</td>
<td>None</td>
</tr>
<tr>
<td>35</td>
<td>N</td>
<td>33</td>
<td>91</td>
<td>None</td>
</tr>
<tr>
<td>36</td>
<td>N</td>
<td>28</td>
<td>28</td>
<td>Prednisone 20 mg/d</td>
</tr>
</tbody>
</table>

*Some patients in this group were receiving corticosteroids and/or other treatments when beginning IVGG (Table 1). Platelet counts x 10^3/μL.

Table 4. Comparison of Outcome of Maintenance IVGG With the Peak Count After the Initial Infusion

<table>
<thead>
<tr>
<th>Outcome of Maintenance</th>
<th>N</th>
<th>Peak Platelet Count*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>REM</td>
<td>5</td>
<td>210.0</td>
</tr>
<tr>
<td>SWT</td>
<td>11</td>
<td>144.3</td>
</tr>
<tr>
<td>M</td>
<td>13</td>
<td>231.4</td>
</tr>
<tr>
<td>REF</td>
<td>11</td>
<td>204.2</td>
</tr>
</tbody>
</table>

*Platelet count x 10^3/μL.
who required repeated infusions. The platelet count is depicted on the Y axis and time is shown on the X axis. IVGG infusions are indicated by vertical lines at the top of the figure. Note that this patient received a number of infusions of IVGG before suddenly entering a lasting REM.

Increases <100,000 and only one patient in this group was initially unresponsive to IVGG; the platelet increase in this group averaged 204,200/μL (Table 4). The nine initially responding patients who then became unresponsive to IVGG maintenance, did so at intervals from 2 weeks to 3 months after their initial treatment.

The outcomes described were achieved by infusing 644 g of IVGG per patient, reflecting a cost, for the gammaglobulin alone (at $35.00/g) of more than $22,500 per patient. Infusion charges were not considered in this calculation.

Chronic nonsplenectomized patients. Of the ten chronic nonsplenectomized patients, none achieved REM, five became SWT, four required continued M, and one became REF to IVGG. The five latter patients whose outcomes were M and REF underwent splenectomy. Less IVGG was infused per patient in the nonsplenectomized patients since the investigators recommended splenectomy to these patients if repeated infusions of gammaglobulin were required.

Therapy before receiving IVGG. Thirty of 40 patients received IVGG after failing splenectomy. Of these 30 patients six had also received prednisone, seven had received prednisone plus one additional agent, seven had received prednisone plus two additional agents, and ten patients had received prednisone plus three or more additional agents before beginning IVGG (Tables 1 and 5). There is a trend suggesting that the more previous treatments a patient had received, the less well he would respond to IVGG (Table 5), but this trend did not achieve statistical significance (P > .05). Three of the ten patients who had failed splenectomy as well as prednisone and three or more additional therapies still had good responses to IVGG (two SWT, one M) demonstrating that IVGG may be effective in even the most refractory patients.

Alternate therapies to IVGG for unresponsive patients. Ten of the 30 previously splenectomized patients (32%) could not be successfully maintained despite repeated 0.8 to 1 g/kg infusions of IVGG. Many of these patients had received (and been shown to be refractory to) “conventional” agents before beginning IVGG. The combination of IVGG with a high-dose, 60 mg, of alternate-day prednisone was a useful strategy for patients initially responsive to IVGG who then became unresponsive or who continued to require maintenance therapy at 2-week intervals. Using this approach, six of ten patients on combined IVGG/prednisone required IVGG infusions at intervals of >2 weeks to maintain a platelet count >20,000/μL. Subsequently, four of these patients no longer required IVGG therapy. Two became stable on 15 mg of prednisone every other day and the other two are currently tapering their dose of alternate-day prednisone. The other two responsive patients now require maintenance IVGG at 4- to 6-week intervals.

Conventional therapy at standard doses (Danazol, 800 mg/d for 4 to 6 weeks; cyclophosphamide, 150 mg/d for 4 weeks; azathioprine, 100 mg/d for 4 to 6 weeks; and repeated four- to five-hour infusions of vinblastine at 6 mg/m²) all failed to induce platelet responses on the 11 occasions in which they were tried in the splenectomized patients refractory to IVGG.

**DISCUSSION**

Splenectomy remains the mainstay of ITP therapy in adults; 70% to 90% of patients who develop severe thrombocytopenia will require splenectomy and most will respond to it. Many patients will not require therapy after splenectomy even if they have not achieved REM. However, those patients with persistently low platelet counts <20,000/μL and signs of hemorrhage (perhaps ≤10% of all patients) do not have an optimal treatment available to them, and some patients eventually die from hemorrhage as did three REF patients in our own series (no. 9, 25, and 27).

<table>
<thead>
<tr>
<th>Response</th>
<th>Prednisone Only</th>
<th>Prednisone +</th>
<th>Prednisone +</th>
<th>Prednisone +</th>
</tr>
</thead>
<tbody>
<tr>
<td>to IVGG</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SWT</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>M</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>REF</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
IVGG did not appear sufficiently effective in non-splenectomized chronic patients, in view of the limited results and the quantity of gammaglobulin required, to recommend deferring splenectomy. However, IVGG was effective enough in these patients, 50% became SWT, to merit consideration in patients with a medical reason to avoid splenectomy. However, IVGG was effective in splenectomized patients with chronic ITP raises the possibility that repeated high-dose IVGG may have an effect on the natural history of the disease. Data in support of this hypothesis has recently been reported by Imbach et al, who found that children with acute ITP treated initially with IVGG achieved permanent REM significantly sooner than those treated initially with prednisone.21 In addition, several studies of the mechanism of the IVGG effect have suggested that the therapy has an immunomodulatory effect, leading to decreased antiplatelet antibody production in those patients with good responses.22,23 Such an effect might be caused by repeated infusion of antiidiotype antibodies to the antiplatelet antibody in a manner analogous to that reported with autoantibodies to factor VIII.24

Even in the absence of a curative effect, a major advantage of IVGG is that it probably is the least toxic M therapy. IVGG toxicity appears to be largely limited to postinfusion headaches, which can be managed by using acetaminophen and diphenhydramine as needed for such a reaction and then before and after subsequent infusions. Despite reports of hepatitis occurring with investigational gammaglobulin preparations,26-27 there is little to no risk of developing hepatitis with currently licensed products. Neither AIDS nor seroconversion to HIV has been reported following IVGG.28-29 In addition IVGG infused in premature infants did not impair development of immune function.30

The major drawbacks of IVGG therapy in chronic adult patients have been the need for repeated infusions, the necessity for IV administration, and the cost. Using 1 g/kg maintenance infusions may make IVGG a feasible maintenance therapy. Infusions may initially be required at 2-week intervals, but most patients either improve and require treatment less often or become REF. The cost of using IVGG is substantial and the good results reported here reflect an average infusion of more than 600 g per patient or approximately eleven 60-g infusions per patient. We speculate, in view of the apparent effectiveness of the combination of IVGG infusions and alternate-day prednisone in REF patients and the high cost of IVGG therapy, that a practical approach to IVGG maintenance might be to use alternate-day prednisone with IVGG from the inception of therapy.

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REFERENCES

Maintenance treatment of adults with chronic refractory immune thrombocytopenic purpura using repeated intravenous infusions of gammaglobulin [see comments]

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