Experience With Protein A-Immunoadsorption in Treatment-Resistant Adult Immune Thrombocytopenic Purpura

By Harry W. Snyder, Jr, Sharon K. Cochran, Joseph P. Balint, Jr, Juergen H. Bertram, Abraham Mittelman, Troy H. Guthrie, Jr, and Frank R. Jones

Extracorporeal immunoadsorption of plasma to remove IgG and circulating immune complexes (CIC) was evaluated as a therapy for adults with treatment-resistant immune thrombocytopenic purpura (ITP). Seventy-two patients with initial platelet counts <50,000/µL who had failed at least two other therapies were studied. They received an average of six treatments of 0.25 to 2.0 L plasma per procedure over a 2- to 3-week period using columns of staphylococcal protein A-silica (PROSORBA® immunoadsorption treatment columns; IMRE Corp, Seattle, WA). The treatments caused an acute increase in the platelet count to >100,000/µL in 18 patients and to 50,000 to 100,000/µL in 15 patients. The median time to response was 2 weeks. Responses were transient (<1 month duration) in seven of those patients (10%), but no additional relapses were reported over a follow-up period of up to 28 months (mean of 8 months). Clinical responses were associated with significant decreases in specific serum platelet autoantibodies (including anti-glycoprotein Iib/IIIa), platelet-associated Ig, and CIC. Thirty percent of treatments were associated with transient mild to moderate side effects usually presenting as a hypersensitivity-type reaction. Continued administration of failed therapies for ITP, which always included low-dose corticosteroids (≤30 mg/d), had no demonstrable influence on the effectiveness of immunoadsorption treatment but did depress the incidence and severity of side effects. The degree of effectiveness of protein A immunoadsorption therapy in patients with treatment-resistant ITP is promising and further controlled studies in this patient population are warranted.

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IMMUNE THROMBOCYTOPENIC purpura (ITP) in adults is an autoimmune disorder in which platelets are sensitized by association with antiplatelet antibodies and/or circulating immune complexes (CIC) making them susceptible to removal from the circulation by reticular macrophages in the spleen. Specific autoantibodies to platelet structural glycoproteins (GPs) or glycosphingolipids, antibodies to foreign antigens nonspecifically adsorbed to platelets, and CIC adsorbed to platelet Ig-Fc or complement receptors have all been shown to contribute to development of ITP. This qualitative diversity among platelet-directed Ig, coupled with the observation that the disease in adults often coexists with other diseases of the immune system such as systemic lupus erythematosus and autoimmune hemolytic anemia, suggests that adult ITP is a disorder of immunoregulation. However, specific instigators of the disease in adults remain obscure and the onset is usually insidious. Depending on the severity of the resulting thrombocytopenia, the most common manifestations of ITP range from easy bruisability and petechiae to epistaxis and gingival bleeding to, more rarely, anal, gastrointestinal, or intracranial bleeding. Spontaneous remissions in adult ITP are rare, occurring in less than 5% of patients.

In the absence of a known direct cause of ITP the aim of conventional therapy has been to limit the platelet-clearing activity of the spleen. The major treatment modality is glucocorticosteroids followed by splenectomy in those patients who fail to obtain a permanent unmaintained response. Patients who fail both steroids and splenectomy also tend to be resistant to other forms of treatment including vinca alkaloids, danazol, colchicine, ascorbic acid, cyclophosphamide, azathioprine, and high-dose intravenous gamma globulin (IV IgG). These chronic refractory patients are at much greater risk for morbidity and mortality from their disease (16.6% mortality v 3.9% to 4.4% during follow-up evaluation of all chronic ITP patients). Alternative approaches to therapy need to be evaluated in this high-risk population.

Recently, protein A immunoadsorption treatment columns have become commercially available for use in the therapeutic removal of IgG and IgG-containing CIC from plasma of patients diagnosed as having ITP with platelet counts less than 100,000/µL. In preliminary studies, mostly with human immunodeficiency virus (HIV)-associated thrombocytopenia, immunoadsorption treatments were shown to be effective in diminishing CIC and platelet autoantibodies, in increasing levels of second antibodies that neutralize autoantibody activity in vitro, and in normalizing platelet counts. This report summarizes extensive multicenter experience with this new modality for treatment-resistant ITP.

PATIENTS AND METHODS

Patient selection. At the time of ordering immunoadsorption treatment, physicians were requested to participate in a study following the progress of patients over a 2-year period. Case record forms were provided for gathering detailed information regarding patient demographics, date of initial diagnosis of ITP, dates and doses of administration of therapy, response(s) to previous therapy, current status of the patient (laboratory values and physical findings including extent of hemorrhagic symptoms and concomitant disease), and treatment plan (volumes of plasma to be treated, frequency of treatments, use of concomitant therapies). The amount of information actually received varied widely from patient to patient. For the purposes of the present analysis only patients with complete histories and confirmed treatment-resistant ITP were considered: all patients failing corticosteroids and...
with failure of at least two therapies, platelet counts less than 50,000/µL, no other condition that could account for low platelets (eg, splenomegaly, infection, drug use, or neoplasia), normal or increased number of megakaryocytes in bone marrow biopsies, hemorrhagic symptoms. Patients who received concomitant therapy, most often tapering doses of corticosteroids, were included in the evaluation but they were, for the most part, analyzed separately.

In total, the experiences of 72 patients who received treatment at 45 different institutions in the United States were evaluated.

**Treatment device.** Sterile treatment columns containing 200 mg of highly purified protein A covalently bound to a silica matrix (PROSORBA columns; IMRE Corp, Seattle, WA) were used.25 The columns were extensively washed using 4 L of sterile saline followed by 0.5 L of sterile saline containing 5,000 U of heparin immediately before perfusion of patient plasma. A new column was used for each treatment. Protein A binds the Fc fragment of IgG having a greater affinity for immune-complexed IgG.26

**Treatment procedure.** Patients received treatment of either 250 mL or 1,000 to 2,000 mL of plasma. For the patients receiving treatment of 250 mL of plasma, 1 U of blood was removed by phlebotomy and the plasma was separated from the cellular elements by centrifugation ("off-line" procedure). The remaining patients had larger volumes of plasma treated after separation from the cellular elements using an apheresis machine ("on-line" procedure). During both modes of treatment plasma was perfused through the columns and returned to the patients at a rate of 10 to 20 mL/min. The goal of treatment was to achieve a platelet count of at least 50,000/µL. An initial regimen of six treatments over a 2- to 3-week period was recommended. Forty-three patients received immunoadsorption treatments only. Twenty-nine patients who were not responding to other therapies for ITP continued on those therapies while immunoadsorption treatment was administered concomitantly. Twenty of these patients received only low-dose corticosteroids (≤30 mg/d), while nine patients continued with a combination of low-dose corticosteroids and other drugs (danazol, five patients; vincristine, three patients; cyclophosphamide, one patient).

**Response evaluation.** Patients were evaluated for response, time to response, and duration of response in the presence or absence of "maintenance" doses of corticosteroids (≤30 mg/d). Evaluations were made before treatment, at the time of each procedure, at least once during an initial follow-up period of 1 month, and every 3 months thereafter for up to 2 years. Platelet counts and all serologic test results were determined using blood samples collected immediately before each treatment. Because the signs and symptoms of hemorrhage gradually disappeared as platelet counts increased, the primary objective measurement of clinical response was quantitative increase in platelet count. A "fair response" was defined as at least a doubling of the baseline platelet count and achievement of a count in the range of 50,000 to 100,000/µL. A "good response" was defined as achievement of a count of greater than 100,000/µL. Responses maintained for less than 2 months were termed "transient." All other responses were referred to as "durable." Relapses were defined as a decrease in platelet count to <50,000/µL which required immediate therapeutic intervention or which was sustained for at least 1 week without rebounding in the absence of intervention.

**Immunologic assays.** Levels of platelet-associated Ig (PAIg) and serum platelet-directed Ig (PDIg) were determined using enzyme-linked immunoadsorbent assays (ELISA) as described previously.26,27 PAIg and PDIg levels measured in a panel of 21 normals averaged ± standard deviation) 5 ± 2 ng/10^10 platelets and 0.2 ± 0.1 µg/mL, respectively. Positive results were defined as measurements >2 SD above the normal range (proportionally, PAIg > 10 ng/10^10 platelets and PDIg > 0.5 µg/mL). Because the above assays do not distinguish between IgG and CIC binding to platelets, sera were also evaluated for levels of antibody to the purified GPIIb/IIIa complex of human platelet membrane GPIIb by ELISA. As in the standard PDIg test, positive results were defined as greater than 0.5 µg/mL.

Total Clq-containing CIC in serum samples were also quantitated using an ELISA test system (Immunomedics, Newark, NJ). Standards of quantitated amounts of Clq-bound aggregated human IgG were included with each test and positive results were defined as values greater than that of the standard with the lowest concentration (10 µg/mL).

Proteins adsorbed onto posttreatment columns were eluted by washing with phosphate-buffered saline, pH 11.5, and eluates were neutralized by addition of 0.1N HCl. Levels of IgG were quantitated by single radial immunodiffusion on thin-layer agarose plates containing monospecific antiserum (Behring Diagnostics, La Jolla, CA). Levels of PDIg and CIC were quantitated as described above.

**Toxicity evaluation.** Toxicity or other adverse experience was evaluated for each treatment. Patients who received concomitant therapy were considered independently from those who only received immunoadsorption treatment. The severity of individual side effects was evaluated according to a grading scale based on the Common Toxicity Criteria developed by the National Cancer Institute. In general, grade 1 was mild (usually transient, requiring no special treatment and not interfering with usual daily activity), grade 2 was moderate (may be ameliorated by simple therapeutic maneuvers, requires usual activity), grade 3 was severe (requires therapeutic intervention, interrupts usual activities, hospitalization may be required), and grade 4 was life threatening (requires hospitalization).

**Statistical methods.** Patient baseline characteristics were compared between treatment groups for balance using the chi-square and t-tests for discrete and continuous variables, respectively. Certain contingency tables had sparse entries in some categories. In those cases categories were pooled into smaller tables for valid chi-square analysis.

Quantitative data were reported as medians, ranges, and means ± standard error. Comparisons of sample means were made using the two-sample t-test for unpaired observations and the paired t-test for linked observations.

The influence of patient-related factors on response was evaluated by allocating patients into subgroups, ranking the responses (good > fair > none), and comparing the relative effectiveness of the therapy using the Mann-Whitney two-sample rank test. Responses of patients in each subgroup were compared with responses of all other patients in the group. In cases where entries in some subgroups were sparse (eg, young and old patients) larger subgroups were formed. The influence of treatment-related factors on response was evaluated similarly. Patients were allocated into four subgroups based on treatment regimen (on-line or off-line mode with or without concomitant therapy) and the relative effectiveness demonstrated in each subgroup was compared with that in all other patients of the group. By combining subgroups, comparisons of effectiveness related only to treatment mode or use of concomitant therapy were also made.

The influence of patient-related and treatment-related factors on toxicity was also evaluated using the two-sample rank test. Toxicity grades were ranked from 1 to 4 as described above.

Correlations between quantitative levels of CIC, PDIg and PAIg, and logarithmically transformed platelet counts were analyzed by linear regression. The significance of correlation coefficients (r) was evaluated using the t-test.
RESULTS

**Patient population.** The baseline characteristics of patients reviewed for this report are shown in Table 1. All patients were adults, the youngest being 18 years old. Four of the patients were homosexual males with HIV-associated thrombocytopenia. Ten patients had ITP of relatively short duration (2 to 6 months) but had already failed to respond to corticosteroids and splenectomy. Sixty-two patients had ITP diagnosed 8 months to 40 years previously (mean 6 years, median 2 years) and had failed two to seven different therapies (mean 4, median 4) including corticosteroids in every case. All patients exhibited hemorrhagic symptoms involving the skin (petechiae, purpura, ecchymoses, and/or easy bruising) with or without obvious involvement of other sites. The mean initial platelet count was 18,000/µL with a range of 1,000 to 49,000/µL.

The patients received one of four possible treatment regimens based on the volume of plasma to be treated and whether or not current unsuccessful therapy would be continued (Table 2). Although patients were not randomly distributed among the treatment regimens, there were no significant differences among the groups in terms of the demographic and disease-related characteristics listed in Table 1.

The effectiveness of the treatment columns in the four procedures in binding IgG (including PDIg) and CIC is also shown in Table 2. On average, the on-line procedure was associated with binding of greater quantities of CIC compared with the off-line procedure ($P = .05$). Otherwise, no significant differences in effectiveness were determined.

**Clinical response.** Overall, 18 patients achieved good responses, 15 patients achieved fair responses, and 39 patients achieved poor or no responses (Table 3, Fig 1). Ten of the 18 good responses were achieved during the first week of treatment and the other eight were attained within 3 weeks. The median number of treatments administered before a good response was two (range 1 to 6) and the mean increase in platelet count was 251,000/µL with a median increase of 193,000/µL (Fig 1). Fifteen fair responses were also achieved within 2 to 4 weeks after a median of three treatments (range 1 to 6) (Table 3, Fig 1). The mean increase in platelet count in these patients was 52,000/µL with a median increase of 46,000/µL (Fig 1).

The effectiveness of the four treatment maneuvers in achieving platelet responses in patients with treatment-resistant ITP was evaluated (Table 3). No one regimen was determined to be significantly more effective than the others; however, there was a strong trend toward treatment of the smaller volume of plasma without concomitant therapy (patient group 1) being the least-effective therapy ($P = .06$). No significant differences in effectiveness based solely on the volume of plasma processed ($P = .31$) or use of concomitant therapy ($P = .24$) were determined (Table 3).

**Prognostic factors.** No relationship was determined between effectiveness of immunoadsorption therapy and pa...
Table 3. Relationship of Variables in Treatment Procedure to Response

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Volume of Plasma Perfused (mL)</th>
<th>Concomitant Therapy</th>
<th>No. of Patients</th>
<th>None</th>
<th>Fair</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>–</td>
<td>16</td>
<td>12</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>+</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2,000</td>
<td>–</td>
<td>27</td>
<td>14</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>2,000</td>
<td>+</td>
<td>16</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>1 + 2</td>
<td>250 or 2,000</td>
<td>– or +</td>
<td>29</td>
<td>17</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>3 + 4</td>
<td>2,000</td>
<td>– or +</td>
<td>43</td>
<td>22</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>1 + 3</td>
<td>250 or 2,000</td>
<td>–</td>
<td>43</td>
<td>26</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>2 + 4</td>
<td>250 or 2,000</td>
<td>+</td>
<td>29</td>
<td>13</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>All</td>
<td>250 or 2,000</td>
<td>– or +</td>
<td>72</td>
<td>39</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

Three deaths attributable to ITP were reported during the follow-up period (cerebral hemorrhage, one patient; gastrointestinal bleeding, two patients). All three patients had failed to respond to immunoadsorption therapy in addition to other treatments. Two of the patients had also been refractory to corticosteroids and splenectomy.

**Side effects.** A majority of patients experienced at least one episode of a side effect during a treatment course, although the majority of treatment procedures were free of adverse effects (Tables 4 and 5). The most common clinical manifestation was a short-lived 1- to 2-hour hypersensitivity-type reaction consisting of fever, chills, and generalized pain occasionally associated with nausea/vomiting and urticaria. This and all other less frequently reported side effects were observed more frequently among treatments involving only immunoadsorption (35%) than among treatment where concomitant therapy was also administered (23%, P < .01). The severity of these side effects, when evident, also tended to be greater in patients receiving immunoadsorption alone (44% grade 1 and 52% grade 2 vs 60% and 37%, respectively, P < .01).

Three treatments were reported to have been stopped because of development of an unmanageable adverse reaction. One treatment was discontinued because of development of hypotension and tachycardia, and two were stopped due to development of a short-term serum sickness-like reaction with no evidence of renal involvement. The patients responded to symptomatic therapy and none exhibited any evidence of long-term treatment-related side effects during the follow-up period.

No relationship was determined between toxicity and any of the patient characteristics summarized in Table 1.

**Immunologic response to immunoadsorption therapy.** Immunologic parameters were evaluated in 22 patients who had achieved a fair or good response to therapy and in 20 patients who did not respond. The patients presented with elevated levels of CIC (34 ± 3 μg/mL), PD Ig (2.3 ± 0.1 μg/mL), and PA Ig (34 ± 3 ng/10⁶ platelets). In general,
Table 4. Relationship of Variables in Treatment Procedure to Toxicity

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Volume of Plasma Perfused (mL)</th>
<th>Concomitant Therapy</th>
<th>No. of Patients</th>
<th>No. of Treatments</th>
<th>Incidence of Side Effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>−</td>
<td>16</td>
<td>109</td>
<td>13 (81)</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>+</td>
<td>13</td>
<td>68</td>
<td>8 (62)</td>
</tr>
<tr>
<td>3</td>
<td>2,000</td>
<td>−</td>
<td>27</td>
<td>190</td>
<td>17 (63)</td>
</tr>
<tr>
<td>4</td>
<td>2,000</td>
<td>+</td>
<td>16</td>
<td>121</td>
<td>11 (69)</td>
</tr>
<tr>
<td>1 + 2</td>
<td>250 or 2,000</td>
<td>− or +</td>
<td>29</td>
<td>177</td>
<td>21 (72)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>2,000</td>
<td>− or +</td>
<td>43</td>
<td>311</td>
<td>28 (65)</td>
</tr>
<tr>
<td>1 + 3</td>
<td>250 or 2,000</td>
<td>−</td>
<td>43</td>
<td>299</td>
<td>30 (70)</td>
</tr>
<tr>
<td>2 + 4</td>
<td>250 or 2,000</td>
<td>+</td>
<td>29</td>
<td>189</td>
<td>19 (66)</td>
</tr>
<tr>
<td>All</td>
<td>250 or 2,000</td>
<td>− or +</td>
<td>72</td>
<td>488</td>
<td>49 (68)</td>
</tr>
</tbody>
</table>

*Highest incidence relative to all other patients (P = .01).
†Lowest incidence relative to all other patients (P < .01).
‡Difference in incidence between groups 1 + 3 and 2 + 4 significant (P < .01).

Platelet counts were inversely related to quantitative levels of these factors (Fig 2).

PDIg in 24 patients was comprised in part of antibodies that bound to purified platelet GPIIb/IIIa. Sera from the other 18 patients had no demonstrable antibodies against GPIIb/IIIa; the target antigen(s) for these patients remains to be determined. The average level of anti-GPIIb/IIIa antibodies in the 24 patients (2.5 ± 0.5 μg/mL) was very similar to the average level of total PDIg (2.6 ± 0.5 μg/mL).

Table 5. Incidence of Side Effect Experienced by ITP Patients During Immunoadsorption Treatments

<table>
<thead>
<tr>
<th>Type of Side Effect</th>
<th>No. of Treatments (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunoadsorption Only (N = 299)</td>
</tr>
<tr>
<td>Allergic</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>41 (14)</td>
</tr>
<tr>
<td>Fever</td>
<td>48 (16)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Pain</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>30 (10)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Swelling/edema</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*Statistically significant difference.

Both responder and nonresponder patients showed significant decreases in CIC and PDIg during immunoadsorption therapy (Fig 3). However, the responder group had relatively lower initial levels of CIC (28 ± 3 μg/mL v 40 ± 6 μg/mL, P = .05) and PDIg (2.0 ± 0.2 μg/mL v 2.6 ± 0.2 μg/mL, P = .03) and their subsequent decreases were to
near-normal levels. This was reflected in a decrease in PAIg to near-background levels in responder patients that was not achieved by nonresponders (Fig 3).

**DISCUSSION**

Decisions among alternative treatments for adult treatment-resistant ITP are based on considerations of duration of treatment, time to initial response, response rate, duration of maintained and unmaintained responses, and short- and long-term toxicity. In terms of these parameters, protein A immunoadsorption compares favorably with other treatments for adult ITP, especially in achievement of long-term clinical benefit. However, the degree of effectiveness and exactly where this therapy should be integrated into the management of adult treatment-resistant ITP remain to be established by a controlled trial and cost/benefit analysis.

**Effectiveness.** Overall, 46% of adult treatment-resistant ITP patients (33 of 72) achieved at least a fair response to immunoadsorption treatments (Table 3). Spontaneous remissions are unlikely to have made a significant contribution to these responses because they have been shown to occur in less than 5% of a large series of patients with adult ITP.

Only 10% of patients (7 of 72) attained responses which turned out to be transient (<30 days duration). The probability of a patient achieving an unmaintained response lasting at least 2 years was estimated at 36% (95% confidence interval of 25% to 47%). Unmaintained responses of this estimated duration are unusual with other treatments for adult chronic ITP including corticosteroids, vinca alkaloids, danazol, azathioprine, and IV IgG.

Responses were obtained rapidly. Thirty-nine percent of responses occurred during the first week of treatment, 85% occurred within 2 weeks, and all responses occurred within 3 to 4 weeks. Only three deaths attributable to ITP were reported among the 72 patients followed. All three patients were refractory to immunoadsorption therapy in addition to other prior and subsequent treatments. The mortality rate in this series (4.2%) compares closely with mortality rates of 3.9% and 4.4% observed in other large series of patients with chronic ITP. Two of the deaths in the present series occurred among 49 patients who were previously unresponsive to corticosteroids and splenectomy.

**Dose.** Dosage was considered to be dependent on two factors: the volume of plasma treated and the total number of treatments administered over a 3- to 4-week period. No significant difference in effectiveness was demonstrated on the basis of plasma volume treated (Table 3). A maximum of six treatments was sufficient to obtain all but 1 of the 33 responses observed in the series of 72 patients. Nine patients received more than six treatments (an average of 9, median of 10) and only one of those patients responded (after 12 treatments). Although this was a good response, with platelets increasing from 45,000 to 248,000/µL with a duration of greater than 19 months, the low response rate in patients requiring more than six treatments and the cost must be considered in making a treatment decision, especially if alternatives have not been exhausted.

**Concomitant therapy.** Overall, no significant differences in effectiveness were seen in comparison of patients who received immunoadsorption treatment alone and patients who received combination therapy. This was not unexpected because the patients were not responding to corticosteroids (alone or in combination with other drugs) at the time immunoadsorption treatment was begun. A possible exception was a trend toward the off-line mode of treatment alone being the least effective regimen for adult treatment-resistant ITP. This possibility needs to be evaluated further in a controlled trial.

**Prognostic factors.** The only demographic or disease-related characteristic with a demonstrable link to response was baseline platelet count, with patients having initial counts of 20,000 to 50,000/µL faring somewhat better than patients with initial counts of less than 20,000/µL. This finding mirrors the probable immunologic response to immunoadsorption therapy-lowering levels of platelet-binding IgG and CIC. Patients with higher initial platelet counts generally have lower levels of these molecules to begin with (Figs 2 and 3) and the treatment is effective in lowering those levels to background (Fig 3). Inverse correlations between PAIg values and platelet counts and between PAIg levels and intravascular platelet life span have been noted by numerous investigators. Initial platelet count

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**Fig 3.** Changes in levels of CIC, PDlg, PAIg, and platelet counts in 42 adults with treatment-resistant ITP who received immunoadsorption therapy. Mean values of samples from 22 patients achieving fair or good responses (●●●●) and from 20 patients classified as nonresponders (○○○○○○) are shown. The hatched lines (■■■■) represent lower-limit positive values for CIC (10 µg/mL), PDlg (0.5 µg/mL) and PAIg (10 ng/10^9 platelets), and low-normal platelet counts (150,000/µL).
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has been shown not to be predictive of response to corticosteroid therapy.29

Safety. Long-term remissions were achieved with a relatively low risk of significant adverse experience. The treatment schedules of only three patients (4%) were interrupted because of adverse experience as compared with the potential of achieving long-term remission in 36% of these high-risk patients. The most common adverse experience, a short-lived hypersensitivity-like syndrome, has also been shown to be associated with administration of other therapies, including interleukin-2 (IL-2) and γ-interferon (γ-IFN), which are used to modulate activity of the immune system. Adverse experience was found to be sensitive to concurrent therapies (Table 5). This is probably attributable to low-dose corticosteroids, which were part of all concurrent treatment regimens. This remains to be established in a prospective trial.

The side effects associated with protein A immunoadsorption therapy (using PROSORBA® treatment columns specifically) compare favorably with those experienced by patients receiving long-term corticosteroid therapy (fluid retention, adrenal suppression, gastric hyperacidity, steroid psychosis, osteoporosis, cushinoid facies, risk of opportunistic infection), danazol (weight gain, seborrhoea, acne, headache, gastric intolerance, liver toxicity, erythema multiformis), vinca alkaloids (peripheral neuropathy, alopecia, constipation, severe hypotension, fever, agranulocytosis, hepatitis), azathioprine (marrow suppression, anorexia, nausea/vomiting, increased risk of lymphoma), cyclophosphamide (marrow suppression, alopecia, hemorrhagic cystitis, hepatic toxicity, sterility, increased risk of acute leukemia), and splenectomy (risk of overwhelming post-splenectomy sepsis syndrome).22

Cost. The cost of immunoadsorption therapy is dependent on the cost of apheresis procedures, and this was found to be highly variable among institutions and geographical areas. The cost of a course of six treatments among a cross-section of 10 institutions averaged $11,370 (range $7,950 to $16,800). There was no significant difference in cost of the off-line versus the on-line procedure. The average cost of a splenectomy was $12,000. The cost of a standard IV IgG treatment of 2 g/kg in a 70-kg patient averaged $9,380. The cost of an induction and maintenance program giving a total of 606 g IV IgG over an average 10-month period30 would be approximately $40,602.

Mechanism. Reduction of platelet-binding Ig and CIC levels in patients' plasma has been the postulated mechanism by which protein A immunoadsorption elicits clinical effects in ITP. However, the relationship of PAig, PD Ig, and CIC changes to platelet responses (Figs 1 through 3) is not likely to be a direct result of bulk removal of these molecules because the binding capacity of treatment columns is approximately 1 g of IgG.26 Therefore, the clinical effect may derive indirectly from an immunomodulation induced during the treatment.

Documented immunologic responses to protein A immunoadsorption treatment include increases in natural killer (NK) cell activity, monocyte IL-1 production and absolute numbers of activated T-helper and B cells, a decrease in absolute numbers of activated T-suppressor cells, and increases in antibodies against viral and tumor-associated antigens.26,31,32 In the case of chronic ITP patients responding to immunoadsorption therapy, significant increases in antiidiotypic GPIIb/IIIα antibodies have been described.26 Recently, Berchtold et al33 also demonstrated antiidiotypic GPIIb/IIIα antibodies in therapeutic preparations of IV IgG. Inhibition of autoantibody binding ranged from 20% to 41% using only a concentration of 3.2% IV IgG, compatible with expected therapeutic concentrations in vivo,34 suggesting that small changes in concentrations of antiidiotypic antibodies induced by any therapy could have unexpectedly dramatic effects on autoantibody activity. These studies also suggest a possible mechanism, idiotypic suppression,34 by which long-term remissions in ITP may be maintained without further therapy.

It has been proposed that removal, or changes in the character, of CIC with immunosuppressive activity during immunoadsorption treatment may be responsible for immuno-modulation.26 However, the precise mechanism remains to be established. The effects of immunoadsorption treatment on other processes that influence platelet counts, such as platelet production and availability or activity of macrophage Fc receptors, have not been evaluated.

The primary modes of action of traditional therapies for ITP are also uncertain. The mechanism of corticosteroid activity has been suggested to be inhibition of autoantibody production by splenic lymphocytes,1,5 inhibition of binding of autoantibody to platelets,35 inhibition of macrophage engulfment of platelets,36 and stimulation of platelet production.37 The mechanism of splenectomy has been proposed as eliminating the site of autoantibody production1,2 and eliminating the major site of platelet elimination.1,37 The activity of IV IgG may directly suppress autoantibody synthesis,33,38 enhance T-suppressor cell function,39 or block macrophage Fc receptors.40,41 Disruption of the integrity of cell membranes by danazol42 has been implicated in decreasing the number of macrophage Fc receptors,43 enhancing T-suppressor cell function,44 and decreasing autoantibody production.45

Conclusion. The patients in this series appeared to have CIC as well as autoantibodies involved in the pathophysiology of their thrombocytopenia. Protein A immunoadsorption was effective in reducing levels of these components and causing long-term remissions in previously treatment-resistant patients. Further understanding of the mechanism of this therapy is required before its maximum effectiveness may be realized. Controlled studies of the safety and effectiveness of immunoadsorption therapy with and without concomitant therapy for treatment-resistant ITP are warranted.

REFERENCES


3. Kelton JG, Gibbons S: Autoimmune platelet destruction:
Idiopathic thrombocytopenic purpura. Semin Thromb Hemost 8:83, 1982
7. Bussell JB: Autoimmune thrombocytopenic purpura. Hema-
11. Woods VL Jr, Oh EH, Mason D, McMillan R: Autoantibod-
ies against the platelet glycoprotein IIb/IIIa complex in patients with chronic ITP. Blood 63:368, 1984
21. Snyder HW Jr, Bertram JH, Channel M, Ernst NR, Balint JP, Jones FR: Reduction in platelet-binding immunoglobulins and improvement in plateau counts in patients with HIV-associated idiopathic thrombocytopenic purpura (ITP) following extracorpo-
25. Snyder HW Jr, Bertram JH, Channel M, Ernst NR, Balint JP, Jones FR: Reduction in platelet-binding immunoglobulins and improvement in platelet counts in patients with HIV-associated idiopathic thrombocytopenic purpura (ITP) following extracorpo-
29. Di Fino SN, Lachant NA, Kirshner JJ, Gottlieb AJ: Adult idiopathic thrombocytopenic purpura. Clinical findings and re-
30. Buscell JB, Pham LC, Aleodt L, Nachman R: Maintenance treatment of adults with chronic refractory immune thrombocytope-
37. Gernsheimer T, Stratton J, Ballem PJ, Slichter SJ: Mechanis-
Experience with protein A-immunoadsorption in treatment-resistant adult immune thrombocytopenic purpura