Intravenous Gammaglobulin Treatment of Chronic Idiopathic Thrombocytopenic Purpura

By James B. Bussel, Robert P. Kimberly, Robert D. Inman, Irving Schulman, Charlotte Cunningham-Rundles, Naikon Cheung, Elizabeth M. Smithwick, Joseph O'Malley, Sylvia Barandun, and Margaret W. Hilgartner

High-dose intravenous gammaglobulin (IVIgG) was given to 12 children and adults with chronic idiopathic thrombocytopenic purpura (ITP) to avoid splenectomy or because they either failed to respond to or required maintenance with high doses of steroids and/or immunosuppressives. The average platelet count increase to initial therapy was 239,500/µl (range 23,000–790,000). A concomitant IgG Fc receptor blockade, measured by IgG-sensitized 51Cr-labeled autologous erythrocytes, was seen in 11 of 11 patients tested, both splenectomized and not splenectomized, lasting 3–4 wk. Six or more months after treatment, 2 children are in remission, 2 children and 2 adults are stable requiring no therapy with platelet counts of approximately 50,000 and 30,000, respectively, 3 children require maintenance IVIgG therapy at 2–10-wk intervals, and 1 child and 2 adults have become refractory to further IVIgG. Splenectomy was not performed in 4 children. Two adults were able to discontinue daily prednisone. The 3 patients who became unresponsive to Swiss Red Cross gammaglobulin (IgSRK) therapy did so in conjunction with a markedly elevated platelet-associated IgG and IgM. Serum IgM increased an average of 103 mg/dl after the IVIgG infusions. No significant side effects were seen.

CHRONIC IDIOPATHIC thrombocytopenia purpura (ITP) is a heterogeneous clinical syndrome characterized by thrombocytopenia for at least 6 mo, accompanied by increased megakaryocytes in the bone marrow and frequently by an elevated platelet-associated immunoglobulin G (PAIgG). The usual therapies, corticosteroids and immunosuppressives, are designed to reduce the autoimmune response and/or inhibit the splenic sequestration of antibody-sensitized platelets. If remission does not occur, if toxic doses of medications are required for maintenance of an adequate platelet count, or if an adequate platelet count cannot be achieved by medical therapy, splenectomy is generally recommended. Splenectomy, however, entails a risk of overwhelming sepsis, especially in children. Furthermore, at least 15% of splenectomized patients do not demonstrate an increased platelet count. In these patients, and all individuals in whom the platelet count falls to less than 20,000/cu mm, the risk of intracranial hemorrhage makes further treatment imperative.

Recently, intravenous gammaglobulin has been used to treat chronic ITP. Based on the observation that gammaglobulin treatment can increase platelet counts in patients with hypogammaglobulinemia and thrombocytopenia, Imbach treated seven children with chronic ITP with high dose Swiss Red Cross gammaglobulin (IgSRK). Good initial response of the platelet count with variable long-term outcomes was observed. The mechanism of action of the IgSRK was not defined, but patients with nonimmune thrombocytopenia, i.e., secondary to aplastic anemia, did not respond. Recently, Fehr et al. demonstrated that IVIgG infusions could cause transient reduction of splenic Fc receptor-mediated clearance of IgG-sensitized autologous erythrocytes in 4 adults; these investigators suggested that this inhibition might be the mechanism of the platelet count increase.

Because of the marked platelet count increases in some patients with ITP given IVIgG, we treated patients with chronic ITP either to avoid performing a splenectomy or to avoid administering high doses of steroids and/or immunosuppressives. The platelet count rose in all patients and in children more than adults. Fc-receptor-mediated reticuloendothelial clearance was inhibited in all patients, splenectomized or not, concomitant with the platelet count increase. Platelet antibodies increased markedly in the patients who eventually became refractory to the IVIgG. Serum IgM increased after IVIgG, suggesting that IVIgG is immunostimulatory.

MATERIALS AND METHODS

Patient Selection

Eight children, less than 17 yr old, and 4 adults were referred for treatment of chronic ITP. All 12 patients have been observed for at
least 6 mo after their initial IVlgG treatment. Chronic ITP was
deﬁned as a platelet count less than 80,000/cu mm for at least 6 mo,
increased megakaryocytes in the bone marrow, and usually elevated
PAIgG. The treatment protocol was approved by the New
York Hospital/Cornell Medical Center Committee for Human
Rights in Research; all patients or their parents signed informed
consents for the IgSRK treatment as well as for the IgG-sensitized
autologous erythrocyte clearance studies.

Swiss Red Cross Gammaglobulin (IgSRK)
The intravenous gammaglobulin preparation was supplied by the
Swiss Red Cross (IgSRK, "Sandoglobulin") and was puriﬁed
from Cohn Fraction II, treated brieﬂy at pH 4 in the presence of traces of
pepsin, and then neutralized prior to lyophilization. It contains a
maximum of 4% dimers, 0.3% aggregates, and 11 mg/dl of IgM. It
was given at a dose of 400 mg/kg/day for 5 consecutive days as a
6% solution over 1.5–4 hr. Booster doses were 400 mg/kg for 1 day;
patient 8 received 8 boosters of 800 mg/kg/day.

Routine Laboratory Tests
Complete blood counts were performed on a Coulter S platelet
counts were done manually if the machine platelet count was less
than 50,000/cu mm. They were done at least twice before the start of
therapy, daily during the IVlgG infusions, and weekly thereafter
(Fig. 1). Electrolytes and liver and renal function tests were moni-
tored before and after IgSRK treatment. Immunoglobulins A, G,
and M were determined by radial immunodiffusion using Meloy
plates; they were measured on days 1 (pretreatment), 3, 5, 8, 15, and
22 of therapy and biweekly thereafter.

Platelet-Associated IgG and IgM
Blood from patients was drawn by venipuncture into plastic tubes
with one-sixth volume acid-citrate-dextrose A (ACDA) as an antico-
agulant. Platelet-rich plasma was prepared after preliminary cen-
trifugation on Ficoll-Hypaque (Pharmacia, Piscataway, NJ). Patients
1 and 2 had the PAIgG determinations performed using whole
platelets; the 10 other patients had their platelet suspensions soni-
cated for 3 min at power 7 (Ultrasonica, Model 350) prior to PAIg
above.

PAIgG and PAIgM were measured by a microtiter solid-phase
radioimmunoassay (MSPRIA), which has been previously
described.12,13 In brief, for PAIgG, puriﬁed human IgG at 1 mg/ml in
phosphate-buffered saline (PBS) is adsorbed onto ﬂexible polyvinyl
microtiter plates. After ﬁrst mixing with the platelet preparation,
excess binding sites in the plastic wells are incubated with121I goat
anti-human IgG (Tago, Burlingame, CA; radiolabeled by chlora-
mine-T method) in diluent in the microtiter plate for 4 hr. The wells
are washed and then cut free with a hot wire, and individually
counted in a Micromedic Systems Gamma Counter. The percent
inhibition of binding of the goat anti-human IgG to the plates by
the platelets is plotted against an IgG standard concentration and
platelet sample dilutions. Using the points of 50% inhibition, the
PAIgG of the platelet samples are calculated in femtogram (fg) per
platelet. Values for PAIgM were obtained by the same techniques
using a goat anti-human IgM antibody (Tago). The normal mean
±1 SD was 3.3 ± 1.0 fg/platelet for PAIgG; a normal value for
PAIgM was <1.0 fg/platelet.

Reticuloendothelial System (RES)
Fc-Receptor-Mediated Clearance Studies
Fc-mediated RES studies were performed with a slight modiﬁca-
tion of previously described techniques.14 All subjects’ erythrocytes
were sedimented, washed 3 times in sterile physiologic saline after
removal of the buoyy layer, standardized to a concentration of 5 ×
10⁹ cells/ml, and radiolabeled with 1–2 μCi of ⁵¹Cr (Amersham/
Searle Corporation, Arlington Heights, IL). The ⁵¹Cr-labeled
erthrocytes were then washed 4 times in physiologic saline and
resuspended to their original concentration. An aliquot of labeled
cells was sensitized with an amount of anti-Rh(D) IgG (kindly
supplied by Ortho Pharmaceuticals, Raritan, NJ) known to mediate
clearance half-time in normals of approximately 30 min. The
anti-Rh(D) preparation was sterile, pyrogen-free, negative for hepa-
titis B surface antigen, and free of IgM as determined by column
chromatography, sucrose density gradient centrifugation, and poly-
acrylamide gel electrophoresis. Following incubation at 37°C for 30
min and washing in physiologic saline, the cells were diluted to a

Fig. 1. Clinical course in relation to IgSRK therapy. The time
course of sequential platelet counts (ordinate) is illustrated with
the initial IgSRK therapy indicated by bars for days 0–4 and by
asterisks for single booster doses. Panels A and B represent
nonsplenectomized children, panel C two splenectomized children,
and panel D four splenectomized adults.
total volume of 10 ml and injected into the subject via a scalp vein infusion set. Survival was calculated by timed serial bleeding at 3, 6, 10, 20, 40, 60, 90, and 120 min after autologous cells were infused.

Measured radioactivity was always at least 98.5% erythrocytes bound. Clearance results were recorded as chromium half-times or the time necessary for 50% of the IgG-sensitized erythrocytes to leave the circulation. The impossibility of accurately measuring the radioactivity at zero time made a simple half-time measurement uncertain. Therefore half-times were determined by nonlinear regression on a PDP 11/70 computer. Since human anti-Rh(D) antibody does not fix Cl in Cl fixation and transfer experiments, and since F(ab')2 fragments of anti-Rh(D) antibody do not mediate erythrocyte clearance, removal of chromium from the circulation is interpreted as Fc-mediated RES clearance.

Since six patients were splenectomized, RES hepatic Fc receptor function was measured by a modification of the above techniques with a fourfold increase in antibody sensitization. Liver scintigraphy has confirmed hepatic uptake of erythrocytes prepared with this technique in splenectomized patients.

Eleven of the 12 patients were Rh-positive, allowing the performance of clearance studies in these subjects. Pretreatment clearance studies were performed within 10 days of the start of IgSRK therapy, and all patients had at least two clearances. Subsequent clearances were performed as indicated in Fig. 2.

The 51Cr-labeled, IgG-sensitized autologous erythrocytes were infused between 1 and 2 hr after the end of the day's IgSRK infusion for the clearances performed during the initial IgSRK treatment. Two additional clearance studies for patient 1 were performed before and 1 day after a single booster infused 8 mo after the initial IVIgG treatment.

Data Analysis

Correlations were ascertained using the Spearman rank correlation coefficient. Means were utilized as a descriptive statistic. The duration of a response to IVIgG was defined as the time during which the platelet count was either more than the pretreatment baseline or more than 20,000/cu mm, whichever was greater.

Remission was defined as the maintenance of a platelet count in the normal range (150,000–400,000/cu mm) without therapy.

Since the IgG-sensitized erythrocyte clearance half-times for nonsplenectomized patients are measured in minutes and for splenectomized patients in hours, the post-IVIgG half-time was compared to the pretreatment clearance half-time in the same patient, which was defined as 100%.

RESULTS

Response to IgG

Clinical information for the 12 patients is given in Table 1. All had a substantial increase in their platelet counts with the 5-day infusion (Table 1 and Fig. 1). The mean platelet rise was 239,500/cu mm above the pretreatment baseline; children averaged an increase of 312,000/cu mm, while the 4 adults averaged an increase of 93,000/cu mm. The peak platelet count occurred within 10 days of the start of therapy in all patients except patient 3, whose peak count was delayed until approximately day 20, a pattern repeated after her single-booster infusion. The rate of subsequent decline in the platelet count was variable from patient to patient, but the duration of the response to the initial IVIgG therapy correlated well with the platelet increase from pretreatment to peak counts, \( r = 0.80, p < 0.01 \). The average duration of response was 48 days, with children averaging 63 days and adults 20 days.

Booster infusions (denoted by asterisks in Fig. 1) were given to all patients except patient 7. The increase in the platelet count with a single booster dose was approximately 40% of the increase in the platelet count with the initial 5-day IgSRK therapy. The peak platelet count after a single booster dose was attained in 2–5 days, and booster treatments were required no more often than at 2-wk intervals in the 9 responsive patients. Currently, 2 children (nos. 1 and 7) are in remission; 2 children and 2 adults (nos. 2, 3, 11, and 12) are stable without any therapy with platelet counts of approximately 50,000/cu mm and 30,000/cu mm, respectively; 3 children (nos. 4, 6, and 10) require periodic booster infusions at 2–10-wk intervals to maintain their platelet counts above baseline or 20,000/cu mm; and 1 child and 2 adults (nos. 5, 8, 9) became refractory to IVIgG after initial responses. No patient with an initial platelet increase greater than 200,000/cu mm (nos. 1, 2, 4, 6, and 7) requires more than a single booster every 6 wk. The 3 refractory patients had an average platelet increase of 115,000/cu mm. Patient 5 became refractory immediately after initial treatment; patient 8 became less responsive to IgSRK over a period of 3 mo, with progressively smaller increases of his platelet count after booster infusions; and patient 9 became refractory after an
Table 1. Patient Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Years w/ ITP</th>
<th>Age</th>
<th>Sex</th>
<th>Medication (Previous Treatment)</th>
<th>Splenectomy</th>
<th>Pre-IgSRK</th>
<th>Post-IgSRK</th>
<th>No. of Days to 1st Booster</th>
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<td>138</td>
<td>22</td>
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</table>

*Died from intracranial hemorrhage.
†Treatment not being given immediately pre-IgSRK.

Patients 1-6 received boosters at platelet counts of 40,000; patients 8-12 received boosters at platelet counts of 20,000 μl.

excellent response to her first booster doses. Patient 5 no longer responds to prednisone, and patients 8 and 9 did not increase their platelet counts with reinstitution of prednisone and cyclophosphamide.

Serum Immunoglobulin Levels

Serum levels of IgG increased substantially with the IgSRK infusions; peak values ranged from 1,500 to 3,400 mg/dl, with a mean increase of 1,400 mg/dl. The platelet response to IVIgG correlated with neither the increase in, nor the rate of decline of, the serum IgG level. Polyclonal increases in serum IgM levels were seen in 10 of 12 patients from 3 to 10 days after the end of the 5-day IVIgG infusions, with an average increase of 103 mg/dl (190 mg/dl in nonsplenectomized patients and 37 mg/dl in splenectomized patients). The 4-yr-old splenectomized child and the splenectomized adult who had received hepatic irradiation were the two patients (nos. 7 and 12) failing to increase their serum IgM after IVIgG. Rheumatoid factor assay by latex fixation was negative in 9 patients tested at the peak of their IgM increase.

Fc-Receptor-Specific RES Clearance

All 11 patients tested (patient 12 was Rh-), whether splenectomized or not, developed a prolonged clearance of IgG-sensitized autologous erythrocytes after IVIgG. Each patient had a concomitant increase in the platelet count. Sequential clearance studies were performed in three patients (nos. 1, 3, and 8) prior to their receiving any booster infusions. The pattern of change of the clearance half-times in response to the IVIgG infusions, as seen in Fig. 2, appears similar in all patients, splenectomized and nonsplenectomized: the maximal Fc receptor inhibition occurs by day 8 and is followed by a steady decline, with return to baseline clearance half-time at approximately 4 wk after therapy. Patient 1 had two additional clearance studies.
before and after a single IVIgG booster and his clearance half-time was prolonged to 206% of baseline by the single booster. The degree of inhibition of Fe-receptor-mediated clearance and the increase in the platelet count did not correlate.

**Platelet-Associated Immunoglobulin G (PAIgG and PAIgM)**

The PAIgG and PAIgM values during the first 3 wk of IVIgG therapy, as well as the medians for all PAIG determinations, are shown in Table 1: Patient 8 did not have a pretreatment PAIg determination. Patients 1, 3, and 7 had elevated PAIgG at the time of their diagnoses of ITP, although the initial values during the study period, while they were on immunosuppressive medication, were normal. PAIgG and M did not show any consistent change with IVIgG therapy. No evidence for an increased threshold of clearance of sensitized platelets or of nonspecific binding of immunoglobulin to platelets was seen;9 PAIgG did not increase during the first 3–5 days of IVIgG therapy, except in patient 12.

Persistent marked elevations of PAIgG and PAIgM were clearly associated with the development of eventual unresponsiveness to IVIgG in patients 5, 8, and 9 (Table 2). Patient 9 had elevated PAIgG and PAIgM prior to IVIgG therapy; patient 5 first developed elevated PAIgG and PAIgM after his IVIgG therapy was completed. Patients 10 and 11 were the only other patients with persistent marked elevation of PAIgG and M; their platelet counts were the lowest of the nonrefractory patients.

**Toxicity**

No side effects requiring cessation of therapy were encountered during this study. Five patients (nos. 2, 3, 6, 10, and 12) had headaches occurring at the end of infusion; one patient (4) had a transient episode of pallor and malaise at the end of his first infusion; and one patient (8) with preexisting hypertension became more hypertensive during 2 of 5 infusions. All other clinical parameters and laboratory tests were unremarkable. No side effects were detected with the single-booster infusions, except for mild headaches in patients 3 and 6.

**DISCUSSION**

IVIgG was effective in treating children and adults with chronic ITP in this study. All patients had substantial increases in their platelet counts with the

<table>
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<th>Patient No.</th>
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<th>PAIgM</th>
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<tr>
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<tr>
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<td>16</td>
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PAIgG and PAIgM in femtogram/platelet. PAIgG normal <5.3, PAIgM normal <1.0. All values from the morning before that day’s IgSRK (if given). Median PAIgG and M obtained from all determinations during treatment period; n is the number of determinations.

* Booster IgSRK dose given before these values were obtained.
initial 5-day course of therapy, allowing discontinuation of their immunosuppressive medications. Children had better outcomes after IVIgG therapy than did adults, since 6 of 7 children maintain their platelet counts with or without additional IVIgG, while only 2 of 4 adults have remained responsive. Four children (nos. 1, 2, 4, and 6) were not splenectomized due to their success with IVIgG; one child (no. 7) and two adults (nos. 11 and 12) discontinued corticosteroids.

Published experience of IVIgG therapy of chronic ITP of childhood is limited to Imbach et al.,2 in their study, one child entered remission, five children (including their three splenectomized patients) required maintenance therapy, and one child became unresponsive to further treatment. Treatment of splenectomized adults with chronic ITP has been reported by Schmidt et al.,20 who obtained good initial responses in two of four patients. Both of these results are comparable to our own, indicating that, while adults do not have as good a response to IVIgG as children, most children and some adults will derive long-term benefit from IVIgG treatment.

The development of resistance to the infusions after good initial responses was associated with markedly increased PAIgG and PAIgM levels. Markedly elevated PAIgG and M could overcome the relative RES Fc receptor blockade; or conceivably, the PAIgM could circumvent the IgG Fc receptor inhibition by IgM-mediated complement fixation on the platelet surface, allowing participation of the C3b receptor in sensitized platelet clearance from circulation.21

The result of the evaluation of parameters other than age that might have had prognostic significance for response to IVIgG was inconclusive. Pretreatment PAIg levels did not appear to influence the outcome of therapy. Splenectomy could not be evaluated in this series separately from age. Neither quantitation of Fc receptor blockade per se nor measurements of serum IgG and IgM levels correlated with the ultimate outcome. The correlation between the initial platelet count increase and the duration of response aids in predicting the outcome only after the initial IVIgG therapy.

The mechanism underlying the increase in platelet count associated with IVIgG infusions is complex. Shulman demonstrated that blockade of the RES induced by intravenous injection of red cell stroma could increase platelet counts in ITP,3 and Fehr et al.9 demonstrated that four of their nonsplenectomized patients with acute ITP treated with IVIgG had transient blockade of Fc-receptor-mediated clearance. The apparent necessity for an IgG molecule with an intact Fc region in one patient supports the idea that Fc receptor blockade may be one mechanism of action.7

This study confirms that IVIgG infusions induce Fc-receptor-mediated RES blockade coincident with the increase in the platelet count. The smaller degree of blockade concomitant with a smaller increase in the platelet count after a single booster in patient 1, compared to his original 5-day infusion, suggests the possibility of a dose-response relationship further substantiating this mechanism. The 3–4-wk duration of the Fc receptor inhibition suggests that this blockade could underlie a prolonged increase in the platelet count. The lack of correlation between the prolongation of sensitized erythrocyte clearance and the increase in platelets is not surprising in this group of patients, especially since the “post” clearance studies were performed after different doses of IVIgG. Many other factors, varying from patient to patient, including the degree of platelet sensitization and the rate of platelet production, may contribute to the net platelet count resulting from the interaction of platelets with the RES. The peak effect on the platelet count may also lag several days behind the change in the RES, as is seen with the platelet response to single booster infusions.

The persistence of elevated platelets in several patients beyond a 4-wk interval and the fall in platelets despite continued relative Fc receptor inhibition in other patients suggest that other mechanisms, in addition to Fc receptor blockade per se, contribute to the total effect of IVIgG. The decrease in PAIgG in association with IVIgG therapy, seen by Schmidt et al.20 in one patient and in our patients 3, 6, and 7, suggests that antiplatelet antibody synthesis may be decreased in some patients. Also the twice-observed delayed peak platelet count in patient 3 can only be explained by invoking another mechanism of action in addition to Fc receptor blockade.

The basis of the Fc receptor blockade is uncertain. Exposure of macrophages to immune complexes in vitro leads to loss of Fc receptor expression,22–24 and in vivo infusions of soluble immune complexes can cause RES saturation.25 IVIgG contains some small aggregates,10,11 however, it is unlikely that such aggregates could account for both the magnitude and the duration of the observed Fc receptor blockade. In vitro studies demonstrate that monomeric IgG also binds to macrophage Fc receptors, leading to internalization and loss of surface Fc receptor expression.26 These observations have been reconciled with intact macrophage Fc receptor function in the context of normal serum IgG levels by invoking relative binding constants and local factors in the RES microcirculation. Whatever these mechanisms are, they might be overwhelmed by the large and rapid increase in serum monomeric IgG caused by IVIgG therapy.
The polyclonal increase in serum IgM after IVIgG therapy suggests that the IgG infusions may be immunostimulatory: the lesser IgM response in splenectomized patients confirms earlier work.1

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Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura