A Prospective Study of Treatment of Acquired (Autoimmune) Factor VIII Inhibitors With High-Dose Intravenous Gammaglobulin

By Richard S. Schwartz, Don A. Gabriel, Louis M. Aledort, David Green, and Craig M. Kessler

A decrease in inhibitor titer has been reported in some patients with acquired factor VIII inhibitors treated with intravenous gammaglobulin (IGIV). We have conducted a prospective, multicenter study of high-dose IGIV in treatment of this disorder to determine efficacy. Nineteen patients received induction therapy with IGIV, 1,000 mg/kg x 2 consecutive days or 400 mg/kg x 5 consecutive days, followed by maintenance doses at intervals as clinically indicated. A ≥25% reduction in inhibitor titer was observed in 8 of 16 assessable patients, six of whom met the criteria for response. A rapid decline in inhibitor titer over 3 to 4 days was observed in two patients, but in four additional responding patients—two of whom received repetitive maintenance doses of IGIV—the decline was more gradual, with final nadirs being reached several weeks to many months after treatment. The inhibitor disappeared in three patients with low-level inhibitors, less than 1 Bethesda unit (BU). Concomitant therapy with prednisone may have contributed to the response in two of the patients but was not a factor in four patients; the response rate is, therefore, estimated to be between 25% and 37.5%. These results confirm the beneficial effect of IGIV in treatment of some patients with acquired autoimmune factor VIII inhibitors.

ACQUIRED HEMOPHILIA is a rare disorder caused by the spontaneous development of an autoimmune antibody (inhibitor) against factor VIII coagulant protein (FVIIIA: C).1,4 There is a recognized association between development of acquired antibodies to factor VIII and a number of diseases, especially those with an autoimmune basis.1,3 These risk factors include rheumatoid arthritis, other connective tissue diseases, inflammatory bowel disease, malignancy, skin diseases such as pemphigus, drug treatment (particularly with penicillin), and postpartum state. In many cases, the inhibitor is idiopathic.

Circulating inhibitors to factor VIII may lead to an acquired hemophilic state and life-threatening bleeding complications or, in mild cases, may be detected incidentally because of a prolonged activated partial thromboplastin time (aPTT).1,4 Bleeding episodes may occur spontaneously and be severe and life-threatening. The fatality rate is high, reaching 22% in some series.2 Autoimmune inhibitor antibodies to factor VIII, therefore, pose a serious management problem.

Therapy is often difficult and may include treatment with corticosteroids,6 immunosuppressive agents,6,7 and plasmapheresis to reduce the inhibitor titer and administration of large doses of human or porcine factor VIII or substances with bypassing activity to treat hemorrhage.6,9

In 1981, Imbach et al10 made the empirical observation that high doses of intravenous gamma globulin (IGIV) led to a transient increase in the platelet count in children and adults with idiopathic thrombocytopenic purpura (ITP). After additional reports of beneficial effects of high doses of IGIV in treatment of ITP as well as other autoimmune disorders,11-13 Sultan et al14 reported the experience in treatment with IGIV of two patients with autoimmune factor VIII inhibitors, with a rapid and prolonged, although incomplete, suppression of antibody. This report, as well as subsequent reports from other investigators, involved relatively few patients.15-24 We now report the results of a prospective, multicenter study of efficacy of high-dose IGIV in treatment of acquired inhibitors.

MATERIALS AND METHODS

Patients from four participating institutions with demonstrable acquired autoantibodies to factor VIII were eligible for enrollment into a protocol study of treatment with 5% IGIV, pH 4.25 (Gamimune-N; Miles Inc, Berkeley, CA).25 Both patients who had active hemorrhage and those who did not were eligible for study. Patients with genetic hemophilia were excluded from study. The study protocols and informed consent forms were reviewed and approved by the Institutional Review Board at each participating center.

Study Design

Induction treatment regimens. Two different treatment regimens were used for induction therapy: IGIV 1,000 mg/kg on each of 2 consecutive days or 400 mg/kg or each of 5 consecutive days. In general, the 5-day treatment regimen was used when volume overload was a consideration; otherwise, the 2-day regimen was used.

Definitions of response. A complete response (CR) was defined as complete disappearance of the inhibitor antibody and normalization of the plasma factor VIII level. A favorable response (FR) was defined as a decrease in titer of the inhibitor antibody of ≥50% of the baseline value or a rise in factor VIII to greater than 25%. A partial response (PR) was defined as a decrease of 25% to 49% of the inhibitor titer or, in patients with a baseline factor VIII level of less than 5%, a rise in factor VIII to 6% to 25%. Patients who demonstrated a decline in inhibitor titer ≥24% of the initial baseline value, whose inhibitor decline was not sustained for more than 2 days, or whose final plasma factor VIII level was less than 5% were classified as failures.

Maintenance therapy. Patients continued to receive maintenance therapy with IGIV as determined by their clinical response as follows. (1) No additional therapy was administered for patients who achieved a CR. (2) Patients who achieved an FR could receive IGIV maintenance therapy at intervals as dictated by their inhibitor ...

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antibody response, but no more often than once every 7 days to maintain the inhibitor response. (3) Patients who achieved a PR could continue to receive IGIV maintenance therapy to maintain the improvements in their inhibitor titer. (4) Patients who did not respond to IGIV induction therapy could receive additional courses of IGIV for 2 months to demonstrate failure to respond to therapy.

The maintenance program was a single dose of IGIV, 400 mg/kg; in four patients, one maintenance course of IGIV, 1,000 mg/kg, was administered on 1 or 2 consecutive days. Nine different lots of IGIV were used in the investigation.

**Laboratory Tests**

Plasma samples were processed, stored, and assayed for factor VIII by one-stage clotting assays. Assays for factor VIII inhibitor were performed in the laboratories of the individual participating principal investigators according to the Bethesda method. Any plasma sample found to have an inhibitor level of ≥0.6 Bethesda units (BU) was considered to be positive for factor VIII inhibitor. Bethesda assays were drawn after the last dose of IGIV induction dose and weekly thereafter as appropriate, until no further decrease occurred for two consecutive values or the titer began to increase.

**RESULTS**

Nineteen patients with acquired inhibitors were treated. Clinical details on all 19 patients are summarized in Table 1. In all 19 cases, the inhibitors had been detected because of bleeding symptoms.

**Table 1. Characteristics of Patients Treated With IGIV**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Other Diseases</th>
<th>Symptoms at Diagnosis of Inhibitor</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Response to Prior Therapy</th>
<th>Age at Diagnosis of Inhibitor (yr)</th>
<th>Age at Start of Treatment With IGIV (yr)</th>
<th>Interval From Diagnosis of Inhibitor to Treatment With IGIV</th>
<th>Other Diseases</th>
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</thead>
</table>
| 1           | F   | Systemic lupus erythematosus | Gastrointestinal bleeding | Pred, Aza, Cy | N | 40 | 40.4 | 140 d | Other Diseases
| 2           | F   | Inhibitor postpartum | Postpartum hemorrhage | Pred | N | 32.6 | 38.8 | 6.2 yr | Other Diseases
| 3           | F   | Idiopathic | Postoperative bleeding | Pred, Aza | N | 24.3 | 25.4 | 1.0 yr | Other Diseases
| 4           | F   | Diabetes mellitus | Ecchymoses | None | — | 83.9 | 83.9 | 5 d | Other Diseases
| 5           | M   | Chronic lymphocytic leukemia, asthma; vitamin B12 deficiency | Bleeding after dental extraction | None | — | 66.6 | 68.7 | 28 d | Other Diseases
| 6           | F   | Uterine cancer | Knee hemarthrosis | Pred | Y | 73.4 | 73.4 | 9 d | Other Diseases

**Patients not responding to treatment with IGIV**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Other Diseases</th>
<th>Symptoms at Diagnosis of Inhibitor</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Response to Prior Therapy</th>
<th>Age at Diagnosis of Inhibitor (yr)</th>
<th>Age at Start of Treatment With IGIV (yr)</th>
<th>Interval From Diagnosis of Inhibitor to Treatment With IGIV</th>
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| 7           | M   | Alcoholism, treated tuberculosis, hypertension | Melena, hematemesis, Mallory-Weiss esophageal tear | Cy, plasmapheresis | N | 54.7 | 54.9 | 69 d | Other Diseases
| 8           | F   | Lupus anticoagulant, family history of Hashimoto's thyroiditis and neonatal ITP | Hematuria, subconjunctival and periorbital bleeding | None | — | 83.3 | 83.3 | 2 d | Other Diseases
| 9           | F   | Idiopathic | Thigh bleed | None | — | 48 | 48.8 | 301 d | Other Diseases
| 10          | M   | Prostate cancer | Postoperative bleeding | None | — | 73.1 | 73.1 | 2 d | Other Diseases
| 11          | M   | Diabetes mellitus | Soft tissue bleeding | Pred, Cy | plasmapheresis | 61.6 | 64.2 | 2.6 yr | Other Diseases
| 12          | M   | Griseofulvin for fungus | Bleeding after skin biopsy, submental bleeding | None | — | 59.9 | 60.1 | 58 d | Other Diseases
| 13          | M   | Prostate cancer, congestive heart failure | Extensive bleeding after transurethral prostatectomy | IGIV + Aza | Inhibitor resolved | 74.9 | 77.4* | 2.5 yr* | Other Diseases
| 14          | M   | Idiopathic | Soft tissue ecchymoses | Pred | N | 61.7 | 62 | 90 d | Other Diseases
| 15          | F   | Cardiomyopathy | Hematomas after placement of internal jugular vein catheter; severe airway obstruction | None | — | 76.7 | 76.7 | 2 d | Other Diseases
| 16          | F   | Hypertension | Abdominal pain + hematuria | None | — | 72.2 | 72.2 | 8 d | Other Diseases

**Patients not assessable**

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<th>Patient No.</th>
<th>Sex</th>
<th>Other Diseases</th>
<th>Symptoms at Diagnosis of Inhibitor</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Response to Prior Therapy</th>
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<th>Age at Start of Treatment With IGIV (yr)</th>
<th>Interval From Diagnosis of Inhibitor to Treatment With IGIV</th>
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| 17          | F   | Hypothyroidism | Soft tissue bleed | None | — | 74.3 | 74.6 | 121 d | Other Diseases
| 18          | F   | Osteoarthritis | Soft tissue ecchymoses, massive gastrointestinal bleed | None | — | 86.4 | 88.4 | 1 d | Other Diseases
| 19          | F   | Idiopathic | Development of compartment syndrome after leg injury; postoperative bleeding | IGIV, pH 4.25 | Inhibitor resolved | 55.5 | 56.3* | 290 d | Other Diseases

Abbreviation: Pred, prednisone; Aza, azathioprine; Cy, cyclophosphamide.
* Treated in current series for relapse of inhibitor after initially responding to treatment with IGIV + Aza 3 months earlier.
† Treated in current series for relapse of inhibitor after initially responding to treatment with IGIV, pH 4.25, 8 months earlier.
TREATMENT OF ACQUIRED FACTOR VIII INHIBITORS

Of the 19 patients, 16 were considered assessable, and three patients (patients 17 through 19) were considered non-assessable. Patient 17 received two doses of IGIV, 1,000 mg/kg, with each infusion lasting 9 hours and with the doses separated by 24 hours. After discharge from the hospital and approximately 21 hours after completing the second IGIV dose, she began to develop increasing abdominal girth and flank pain. The patient was treated in a local emergency room, where she was noted to have a blood pressure of 60 mm Hg and was believed to have intraabdominal and/or retroperitoneal bleeding. She was treated with large volumes of fluid resuscitation and then transferred to the University Hospital emergency room, where uncrossed matched blood and factor IX complex concentrate were administered. She became progressively more hypotensive and died in the emergency room approximately 12 hours after symptoms began. Autopsy was not permitted. Patient 18 was treated with IGIV after developing massive gastrointestinal bleeding 2 days earlier that was unresponsive to large amounts of cryoprecipitate and blood; she died 12 hours after treatment, and the response to treatment could, therefore, not be evaluated. Patient 19 had been previously treated with IGIV, 400 mg/kg/d for 5 days, and had responded to treatment as previously reported; she was retreated in the current series for relapse with a low titer inhibitor (0.5 BU) but received only a single dose of IGIV, 400 mg/kg, at induction and was, therefore, not considered assessable.

The 16 assessable patients ranged in age from 25.4 to 83.9 years of age (mean, 62.7 ± 17.0 years; median, 66.4 years). Nine were female and seven were male. Thirteen of the 16

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<th>Table 2. Response to Treatment With IGIV</th>
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<td><strong>Patient No.</strong></td>
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**Abbreviations:** NAV, not available; NA, not applicable.
* Dose is mg/kg × number of consecutive days.
† Doses (mg/kg) administered on separate days.
‡ Number of days after start of IGIV treatment.
§ Data before initiation of azathioprine treatment.
║ Response lasted only 2 days; therefore, patient classified as a nonresponder.
# Patient died approximately 33 hours after treatment.
** Patient died 12 hours after treatment.
assessable patients had underlying diseases, some of which have been reported to be associated with the development of the acquired inhibitor, including systemic lupus erythematosus, asthma, lupus anticoagulant, diabetes mellitus, arthritis, postpartum state, medications, or cancer. In three patients, no associated disorders were present. Four of the six patients responding to IGIV therapy and 4 of the 10 nonresponding patients had been treated with prior immunosuppressive therapy, with only two patients (patients 6 and 13) demonstrating any response. Patient 6 was treated with prednisone, porcine factor VIII, cryoprecipitate, and red blood cell transfusions over 4 days with a decrease in the inhibitor titer from 2.8 BU to 0.2 BU and an increase in the factor VIII level to 53%. However, 6 days after treatment, the inhibitor titer was once again 1.0 BU, at which time treatment with IGIV was initiated with continued prednisone treatment. Patient 13 was treated with IGIV and azathioprine with disappearance of a high-titer inhibitor. However, the inhibitor recurred 3 months after discontinuation of azathioprine, and the patient was, therefore, enrolled in the current investigation.

Of the 16 assessable patients, 12 received induction courses of treatment with IGIV, 1,000 mg/kg/d for 2 days, and four patients were treated with 400 mg/kg/d for 5 days. A ≥25% decline in the factor VIII inhibitor titer was observed in 8 of the 16 assessable patients after treatment with IGIV, six of whom met the criteria for response (Table 2). All responding patients received the high-dose IGIV induction course of 1,000 mg/kg/d × 2.

In three patients (patients 4 through 6) with low baseline level inhibitors (0.9, 1.0, and 1.0 BU, respectively), the inhibitor disappeared completely after IGIV treatment, and three patients (patients 1 through 3) with inhibitor titers of 12, 102, and 280 BU, respectively, achieved favorable responses, with posttreatment inhibitor titers of less than 6 BU. Patient 7 with a high-titer inhibitor had an 83% decrease in the inhibitor titer after IGIV treatment: from 1,228 BU on day 0 to 208 BU on day 7. In patient 15, the inhibitor titer decreased from 4.8 BU on day 0 to 0.3 BU on day 37. However, these two patients were classified as nonresponders because the inhibitor titer remained high without clinical benefit (patient 7) or the response was transient (patient 15). Factor VIII levels were measured in five of the six responding patients (patients 1, 2, and 4 through 6; data not available in patient 3) and became measurable or increased to near normal levels in each of these patients. Peak factor VIII levels lagged behind nadir inhibitor levels, in some cases by many months (Table 2). Two of the responding patients, patients 1 and 6, received concomitant prednisone therapy. Prednisone was initiated at the same time as IGIV therapy in patient 6, but patient 1 had received low-dose prednisone for multiple years, high-dose therapy (35 mg/d) for 2 months before commencement of IGIV treatment, and 37.5 mg/d beginning on day 32 of study (see legend to Fig 1, for full details). As the impact of IGIV on the decrease in inhibitor titer cannot be assessed independently in these two patients, the overall response rate is estimated to be between 25% (4 of 16) and 37.5% (6 of 16) excluding and including these two patients, respectively.

![Fig 1. Clinical course of patient 1: a 40-year-old female with a 10-year history of systemic lupus erythematosus, treated with low-dose prednisone, 2.5 mg daily. The dose was increased to 20 mg daily in October 1986 due to a flare in herpes zoster. She continued on this dosage until September 1987 when she presented with gastrointestinal bleeding. A factor VIII inhibitor of 7.2 BU was diagnosed with a factor VIII level of less than 1%. She was treated with porcine factor VIII and FEIBA; the inhibitor titer subsequently rose to 26 BU (human; 28 BU porcine FVIII). She was briefly treated with azathioprine and cyclophosphamide for several weeks in October 1987, but these drugs were discontinued due to neutropenia. The prednisone dose was increased to 35 mg/d on November 1, 1987. On January 27, 1988, the inhibitor titer was 12 BU, at which time the patient was treated with IGIV, 1,000 mg/kg on January 28 and 29, 1988 (days 0 and 1, respectively, of study). Variable declines in the inhibitor titer were observed after the induction doses of IGIV and subsequent weekly maintenance doses of 400 mg/kg × 6 (a) while continuing the same dosage of prednisone, 35 mg/d (b). After a small increase in the daily prednisone dosage to 37.5 mg/d on day 32 of the study, the inhibitor titer gradually began to decline, decreasing to 6.5 BU on day 40, when the patient received her last dose of IGIV. By day 95, the inhibitor had decreased to 1.9 BU, at which time azathioprine was added, 50 mg/d; the dose was increased to 100 mg/d on day 137. Factor VIII levels (c) were 0 from days 0 to 95. By day 186, the inhibitor titer was 0.25 BU, and the factor VIII level was 2.9%.](image-url)
TREATMENT OF ACQUIRED FACTOR VIII INHIBITORS

In the six patients demonstrating a response (CR, FR, or PR), the time to a ≥25% decline in the inhibitor titer ranged from 3 to 40 days (median, 18 days) for all patients, and 4 to 33 days (median, 18 days) for the four patients who did not receive concomitant prednisone therapy (median decline: 63% for all patients, 71% for patients not receiving prednisone; Table 2). In two (patients 5 and 6) of the three patients with low-titer (≤1.0 BU), newly diagnosed inhibitors treated with IGIV (and prednisone in patient 6), a rapid decline in the inhibitor titer over 3 to 4 days was observed, with complete disappearance within 11 to 14 days of therapy. Two of the other four patients (patients 1 and 2) demonstrating an initial
response received maintenance courses of IGIV treatment. The decline in inhibitor titer continued over a prolonged period of time in these two patients, as well as in two additional patients (patients 3 and 4; Figs 1 through 4). Therefore, the time to ultimate nadir was longer, ranging from 11 to 641 days in all six patients (median, 59 days) and 14 to 641 days (median, 59 days) in the four patients who were treated with IGIV alone without concomitant prednisone therapy. The median final nadir titer posttreatment in the six responding patients was 0.95 BU (0, 0, 0, 1.9, 1.9, and 3.8 BU, respectively). The ultimate response rates (CR, FR, PR) versus initial titer were as follows: initial titer, less than 10 BU: three of five (60%) patients responded; initial titer, 10 to 50 BU: one of four (25%) patients responded; and initial titer, greater than 50 BU: two of seven (28.6%) patients responded. The treatment details of the six responding patients are summarized in Table 2 and are shown graphically by individual patient in Figs 1 through 6.

IGIV was well tolerated, with only 10 reactions reported in 88 infusions (11.4%) occurring in 3 of 19 patients treated overall (16%); one patient accounted for 8 of the 10 reactions. Headache was the most frequent observed side effect, recorded in seven infusions. Other reactions noted in two or less infusions included aching (back, neck, shoulder, and body), dizziness, itching, chest tightness, and wheezing. All reactions were mild or moderate, and none was considered severe. The death of patient 17 approximately 33 hours after completing treatment with IGIV was unexpected and believed to be due to intraabdominal and/or retroperitoneal bleeding with resultant hypotension. It is not possible to determine if this was due to spontaneous bleeding or if the volume of IGIV administered during the preceding 48 hours (20 ml/kg on each of 2 consecutive days) may have contributed to this.

**DISCUSSION**

The present investigation confirms the beneficial effect of high-dose IGIV in some patients with autoimmune FVIII inhibitors, with a ≥25% decline in inhibitor titer observed in 8 of 16 assessable patients, six of whom met the criteria for response. As two of the responding patients received concomitant prednisone therapy, the response rate is estimated to be between 25% and 37.5%, excluding or including, respectively, these two patients in the determination of the response rate. Sultan et al²⁴ have previously reviewed the literature on anecdotal treatment of 11 such patients, 10 of whom demonstrated a greater than 50% reduction in inhibitor titer after treatment. Based on the response criteria used in the current investigation, eight patients would have been classified as having responded to treatment (one with concomitant prednisone). The lower response rate observed in the current study might be ascribed to the fact that it was a prospective rather than retrospective analysis.

As might be predicted intuitively, responding patients in the current series tended to have lower inhibitor titers at treatment, with all three patients who achieved complete remission having initial antibody titers ≤1.0 BU. However, three of the responding patients had high-titer inhibitors (12, 102, and 280 BU, respectively), and in a fourth patient who did not meet the criteria for response, there was a decline in inhibitor from 1,228 BU to 208 BU in 7 days. One of the responding patients had had a high-titer inhibitor of 6 years' duration, so a high-titer inhibitor of longstanding duration is not a contraindication to attempting treatment with IGIV per se. All of the responding patients received the same induction course of IGIV therapy, 1,000 mg/kg ×2 days. The decision as to whether to treat initially with a 2- or 5-day induction course was based on clinical considerations, and, therefore, no conclusion can be made regarding the comparative efficacy of the 2- and 5-day treatment regimens.

A rapid decline in inhibitor titer after IGIV therapy was observed in two patients (one of whom also received prednisone), as has been reported by others,²⁴ but in the other responding patients, the decline was more gradual, with final nadirs being reached much later and sometimes weeks or months after IGIV had been discontinued. The time to a
Fig 5. Clinical course of patient 5. A 68-year-old male was noted to have prolonged bleeding after dental extraction, at which time an inhibitor of 2 BU was detected with a factor VIII level of 11%. Treatment with IGIV began 1 month later, when the inhibitor titer was 1 BU and the factor VIII level was 11%. IGIV, 1,000 mg/kg (▷), was administered on days 0 and 1. Inhibitor titer (O) on day 4 was unchanged at 1 BU, although factor VIII level (○) increased to 17%; repeat inhibitor titer on days 14 and 35 were 0, and plasma factor VIII level increased to 57% and 95%, respectively. No immunosuppressive therapy was administered.

≥25% decline in the inhibiter titer occurred from 3 to 40 days (median, 18 days). As observed in two patients in the current study, repetitive maintenance doses of IGIV over a prolonged period of time may be beneficial in some patients demonstrating an early but incomplete response, resulting in significant late decline in the inhibiter titer. Although it is possible such delayed responses are spontaneous remissions and are not due to IGIV therapy per se, in one of the cases observed in this study, the inhibitor had been present in high titer for 6 years before the gradual decline that began only when IGIV treatment was initiated, suggesting a causal rather than a spontaneous effect.

Treatment with IGIV was generally well tolerated. However, the death of one patient due to presumed intraperitoneal/retroperitoneal hemorrhage approximately 33 hours after completing treatment with high-dose IGIV was unexpected. As a dose of IGIV of 1,000 mg/kg entails a large volume load, such therapy is not recommended for individuals with expanded blood volumes or where fluid volume may be a concern.

Fig 6. Clinical course of patient 6: A 73-year-old female with uterine cancer presented with knee hemarthrosis, at which time a factor VIII inhibitor of 2.8 BU and a factor VIII level of 4% were detected. The patient was treated with prednisone 60 mg/d (III) initially, porcine factor VIII (●), cryoprecipitate (X), and red blood cell transfusions over 4 days, with a decrease in the inhibiter titer (□) from 2.8 BU to 0.2 BU and an increase in the factor VIII level (○) to 53%. Six days after treatment, the inhibitor titer was once again 1.0 BU and the factor VIII level was 26%, at which time treatment with IGIV (▼) was initiated, 1,000 mg/kg on days 0 and 1, with continued prednisone, 30 mg/d, decreased to 20 mg/d on day 3. Repeat inhibitor titer on day 3 was 0.3 BU and on day 11 was 0 BU, with a factor VIII level of 102%. Repeat inhibitor titers during days 11 through 164 were all 0 with factor VIII levels ranging from 59% to 145% on day 164.
Various mechanisms have been postulated for the beneficial effect of IGIV in autoimmune disorders including Fc reticuloendothelial blockade.\textsuperscript{25,26} Inhibition of antibody synthesis,\textsuperscript{10} and increased numbers of suppressor cells.\textsuperscript{27,28} The mechanism responsible for the beneficial effect of high-dose IGIV treatment in acquired FVIII inhibitors is not well understood but may result from antiidiotypic antibodies contained within IGIV against anti-factor VIII autoantibodies.\textsuperscript{24,29-31} IGIV therapy has also been associated with increased suppressor T-cell function in patients with ITP\textsuperscript{27,28} and a patient with a spontaneous inhibitor to factor VIII.\textsuperscript{18} It is possible such effects might contribute to the delayed salutary effect of IGIV observed in some cases.

IGIV therapy is costly and, as demonstrated in the current study, benefits only a minority of patients with acquired inhibitors. It offers, however, an alternative mode of treatment for patients who have not responded to or have become refractory to immunosuppressive therapy, who have demonstrated only partial response to other therapy, who have contraindications to immunosuppressive therapy, or who require treatment for life-threatening conditions.

REFERENCES

A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin

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