

Review article

Intravenous gammaglobulin, 2: pharmacology, clinical uses and mechanisms of action

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Use of IVIG as an immunomodulating agent

Hematologic disorders

Idiopathic thrombocytopenic purpura (ITP) – The use of IVIG in ITP has been well established and reviewed extensively (243–246) and is one of the approved indications of the NIH Consensus; therefore, it will not be discussed in great detail. The effect of IVIG on thrombocytopenia was discovered by Imbach et al. when two immune-deficient patients with infection-related ITP had a marked increase in their platelet count following their routine treatment with IVIG; subsequent evaluation of four additional patients confirmed the efficacy of IVIG (7,247) and this formed the beginning of the use of IVIG to modify autoimmune disease. While the efficacy of IVIG in the therapy of acute ITP is unquestioned, its role in the chronic management of ITP, especially of adults, is still undergoing evaluation. The mechanism of action is not entirely clear, but investigations have led to a much greater understanding of how gammaglobulin can modify autoimmune and inflammatory diseases.

Following the original descriptions of Imbach, a number of controlled studies confirmed that IVIG could result in a prompt rise in the platelet count, and in many patients the increase would persist for long periods (247–249). Some patients would go into a sustained remission but others had a poor response or required frequent infusions in order to maintain their platelet count in a safe range. Even when remission could not be induced, IVIG could be used to defer splenectomy or increase the platelet count acutely to make surgery less hazardous (250, 251). Adults are less responsive than children, but in

some with chronic ITP infusions of IVIG every few weeks can maintain the platelet count (252, 253). It is uncommon for treatment with IVIG to prevent the need for splenectomy in adults as it has in children. The cost of IVIG obviously is much higher in adults and thus the cost: benefit ratio is poorer. In children, use of IVIG to avoid surgery is cost effective up to age 6 (254), after which the higher cost of IVIG outweighs the cost of splenectomy. The medical benefit of avoiding surgery is clear at any age, however. In children with non-life-threatening ITP that is likely to be responsive to a brief course of corticosteroids, therapy with IVIG is probably not necessary or cost effective. However, in more severe or refractory cases the use of IVIG can be life-saving or can prevent a potentially dangerous surgical procedure.

Intravenous gammaglobulin is effective in other forms of thrombocytopenia due to antiplatelet antibodies. Patients who are alloimmunized by repeated transfusions of platelets may become refractory to further infusions. Treatment with IVIG can block the effects of the alloantibody (255–257). Even refractory patients may respond to high doses of IVIG, though those with broadly reactive lymphocytotoxic antibodies were less responsive (258). Infusions of gammaglobulin can be used to treat thrombocytopenia that occurs during pregnancy (259, 260). It is also effective in the management of neonatal thrombocytopenia, which is usually caused by maternal isoantibodies that cross the placenta (261, 262). The fetuses of woman who have a history of thrombocytopenia prior to pregnancy and who have circulating anti-platelet antibodies are at significant risk of developing neonatal thrombocytopenia (263). Treat-

ment of the mother can prevent intracranial hemorrhage in the fetus late in gestation or at the time of delivery. Gammaglobulin can be infused into the mother late in gestation; the IgG crosses the placenta and prevents thrombocytopenia in the fetus (264). Thrombocytopenia associated with HIV infections is also responsive to therapy with IVIG and may avoid the need for immunosuppressive therapy in these already immune compromised patients (195, 265).

The mechanism of action of IVIG in ITP has been studied in detail (266). The rapid rise in the platelet count makes it unlikely that production of autoantibody is decreased, yet many patients enter a long-lasting remission suggesting that immunomodulation has occurred. Salama et al. suggested that trace amounts of anti-A and anti-B IgG binds to red blood cells and the antibody-coated cells are taken-up by the reticuloendothelial system (RES) and block uptake of the platelets (267). RES blockade is still considered to be responsible for the immediate effects of IVIG in ITP and other cytopenias, though it is not known whether the mechanism is antibody-coated red cells (268). There is no *in vivo* evidence that the IgG displaces autoantibody from the platelet. The theory of blockade of the Fc receptor is supported by two other observations, the improvement in ITP when patients are treated either with a monoclonal antibody to the Fc receptor or anti-Rh (D) antibody. Monoclonal antibodies directed against the low affinity FcRIII in mice (269) or humans (270) inhibits Fc activity for several weeks and results in an increase in the platelet count in patients with ITP. Only minute amounts of antibody are required, in contrast to the vast quantities of IVIG required.

The use of anti-Rh(D) was first suggested by Salama based on their theory of antibody-coated red cells and it has since been shown to be effective in several studies (271–273). Bussel and coworkers reported beneficial results of an intravenous form of anti-Rh antibody in 43 Rh+ patients with ITP (274). Multicenter studies are currently underway using this antibody produced in Canada as Winrho-S (Winnipeg Rh Institute, Winnipeg, Canada). The use of anti-Rh(D) has the advantage of not requiring infusions of large quantities of IgG. Only 25 µg/kg, rather than 1 or 2 g/kg, are required. The mechanism of action of anti-Rh(D) may be different than that of IVIG (268, 274). There is a 48-h delay in the onset of the rise in the platelet count when anti-Rh(D) is infused, in contrast to the immediate rise with IVIG. In addition, anti-Rh(D) is not effective in splenectomized patients, unlike IVIG that is equally effective regardless of the presence of the spleen. It is possible that both are acting to modulate Fc activity, but are acting through different mechanisms.

Hemolytic anemia (HA) – The success of IVIG in ITP stimulated its use in other hematologic disorders (275, 276). There were anecdotal reports of successful treatment of autoimmune hemolytic anemia (277, 278), but other reports indicated that the disease was refractory to treatment (267, 279), at least with the 2 g/kg that was used to treat ITP. Bussel et al. used higher doses, 5 g/kg over five days in four patients with refractory HA and achieved a sustained remission in two, a transient response in a third and no response in the fourth (280). Hemolytic anemia was controlled in a patient with common variable immune deficiency who developed HA that responded to, but was dependent on, corticosteroids (281). He was treated with 450 mg/kg for five successive days with a prompt rise in hemoglobin. Therapy was continued with 100 to 200 mg/kg/month with maintenance of the hemoglobin. Four patients with Thalassemia major who developed HA while on a transfusion protocol were treated with 400 mg/kg/day for five days and then 400 mg/kg every three weeks (282). Three of the four had a complete remission and the fourth had a partial response. IVIG was used in combination with methylprednisolone to prevent a transfusion reaction when a women with multiple antibodies to red blood cells required an emergency transfusion of incompatible blood (283).

Intravenous gammaglobulin has been used in other hemolytic diseases. Rubo et al. evaluated the use of IVIG to prevent exchange transfusion in infants with Rh hemolytic disease (284). Thirty two infants were randomly assigned to receive phototherapy alone or in combination with 500 mg/kg of IVIG. Exchange transfusion was performed if the bilirubin exceeded the curves of Poláček by more than 2 mg/dl. Transfusions were necessary in 2 of 16 infants in the IVIG group compared to 11 of 16 infants in the control group. Bilirubin levels were lower in the treated group despite the lack of exchange transfusions. High dose IVIG has also been shown to be of benefit in combination with plasma exchange in severe Rh disease (286). In another approach to Rh disease, a pregnant woman with severe Rh sensitization was treated with IVIG when plasmapheresis failed to adequately lower the levels of antibody (287). The baby was born with a hemoglobin of 12.5 but required several exchange transfusions. There have been no controlled trials of the use of IVIG for transfusion reactions or Rh disease in pregnant women.

Neutropenia – There are a number of case reports and small studies that indicate a favorable response of autoimmune neutropenia to infusions of IVIG. One of the earliest reports was that of a 25 y.o. woman with autoantibodies to neutrophils who responded poorly to corticosteroids and plasmaphere-

sis (288). She had a sustained remission with four doses of 300–400 mg/kg of Sandoglobin®. Six children with severe infections and neutrophil counts $< 300/\text{mm}^3$ were treated with 1 g/kg of IVIG until the neutrophil count reached more than $1000/\text{mm}^3$ (289, 290). The average response required 3 g/kg and lasted 14 days. Recently, a child with autoimmune neutropenia was successfully treated with both IV and IM anti-Rh(D) antibody, similar to the success that has been noted with anti-Rh(D) in ITP (291). This may prove to be a more cost-effective alternative to the use of extremely high doses of IVIG.

Red cell aplasia – Red cell aplasia is characterized by anemia, reticulocytopenia, and absence of red cell precursors. The other marrow elements are normal. It can be shown to be antibody-mediated in about half of the cases. It is often responsive to immunosuppressive drugs, but prolonged courses of therapy may be required and patients often remain transfusion dependent (292). There are numerous anecdotal reports of responses to IVIG. A four-year-old girl with a three-year history of resistant aplasia was treated with 2 g/kg of IVIG over 5 days with only a slight response (293). A second course of IVIG was given one month later and the reticulocyte count increased to 10.5%. The response to each course of therapy was transient, but she responded to subsequent infusions and was no longer transfusion dependent. A more prolonged response was induced in a 30-year-old woman treated with a combination of corticosteroids and IVIG (294). In another case report, a 61-year-old man with aplasia secondary to lymphoma responded to a combination of chemotherapy and IVIG (295), though it is difficult to determine the role of IVIG in this heavily immunosuppressed patient. Four additional patients with red cell aplasia secondary to malignancy also had prolonged remission following therapy with IVIG (296). Infusions of IVIG may be especially beneficial in red cell aplasia that is associated with parvovirus B 19 infection (292, 297). Three additional patients were recently reported who had sustained responses to therapy with IVIG (298). Aplasia was associated with thymoma in one patient, with HIV infection in the second, and was idiopathic in the third, but all had a prompt and prolonged response to 2 g/kg given over five days. All of these reports are anecdotal, and despite apparent benefit, controlled studies are necessary to determine the optimal dose schedule and which patients might respond to IVIG therapy.

Graft-versus-host disease – There have been no studies specifically designed to evaluate the ability of IVIG to modulate GVHD, but in several studies

of the utility of IVIG to prevent CMV infection, it was noted that there was a decreased incidence and severity of GVHD (139). It is difficult to evaluate GVHD alone, as there is a complex interaction between GVHD, CMV infection, prior chemotherapy, and post-transplant immunosuppression. GVHD may intensify CMV infection, and infection may induce GVHD. Nonetheless, in the multicenter trial of 382 patients reported by Sullivan et al. (145), there was a reduction in the incidence of acute GVHD in the patients > 20 years old from 51% to 34% and a decrease in the transplant-related deaths from 46% to 30%. This large study confirmed the previous observations in Seattle (137) and Los Angeles (144). The experience at the Sloan-Kettering in children was similar (150), and overall, the experience in children suggests that the severity and morbidity associated with GVHD is reduced in patients treated with high doses of IVIG (299). It is difficult to compare studies since each has used a different dose, schedule, and IVIG preparation and there have been no controlled studies to indicate what the optimal dose and schedule might be. A recent study indicated that continuous infusions resulted in higher levels of IgG and decreased risk of acute GVHD compared to intermittent infusions (149), but other doses or schedules were not evaluated. One cautionary note was a report by Cottler-Fox & Spitzer who noted an increased incidence of grade II or higher GVHD in 41 patients treated with continuous infusion of Gammagard® compared to 200–500 mg/wk of Gamimune® – N even though there were higher IgG levels and decreased incidence of infections in the Gammagard group (300). They speculated that the greater immunomodulating capacity of the Gamimune® – N might have been due to higher amounts of soluble HLA molecules compared to Gammagard®. These observations must be confirmed, but make the point that all preparations might not be equivalent for every indication and that further controlled studies are urgently needed.

Factor VIII inhibitors – Inhibitors to Factor VIII can arise spontaneously and are a cause of acquired hemophilia, or can be induced in patients with congenital hemophilia as a result of therapy with Factor VIII concentrates. The former are autoantibodies whereas the latter should be more properly considered alloantibodies. Alloantibodies develop in approximately 10% of patients with Factor VIII deficiency as a result of therapy with exogenous Factor VIII; neutralization of the factor decreases its efficacy in the control of bleeding. Infusions of IVIG were not effective in decreasing antibody titers in two patients with alloantibodies (301). In a rather heroic effort, tolerance to Factor VIII was induced by plasmapheresis with extracorporeal adsorption to

protein A Sepharose followed by infusions of IVIG in combination with cyclophosphamide (302).

Spontaneous autoantibody inhibitors to Factor VIII (Factor VIIIc) may occur during pregnancy or postpartum or in association with other autoimmune disorders. Many patients recover spontaneously though the antibodies may persist for long periods of time. The study of these antibodies by Sultan, Kazatchkine, Nydegger, and others, has provided some of the most compelling evidence for the presence of anti-idiotypic antibodies in the regulation of an autoimmune response. (303, 304). Infusions of IVIG into patients with autoantibodies to Factor VIII is associated with an immediate decrease in the titers of autoantibody, but in many patients the effect may persist for more than two years. The immediate effect may be due to neutralization of the antibody, but the long-lasting effect suggests an effect on antibody production. Incubation of patient's serum or F(ab')₂ fragments of the patient's IgG with IVIG results in neutralization of the anti-Factor VIIIc activity. Since the F(ab')₂ fragments are inhibited, the interaction must be mediated by antigen binding sites on the immunoglobulin (304). This suggests that an idio-type-anti-idio-type mechanism must be at work. These investigators also demonstrated that spontaneous recovery from Factor VIIIc autoantibodies is associated with the development of anti-idio-type antibodies that are capable of neutralizing inhibitory antibodies from patients in relapse (305). This further supports the role of anti-idio-type antibodies as part of the natural regulatory mechanism. Treatment with IVIG inhibits autoantibodies in many patients (303, 305), but has failed in some (306). The ability of sera to inhibit the autoantibodies clearly depends on the presence of anti-idio-type antibodies and varies from donor to donor and the incidence of neutralizing anti-idio-type antibodies appears to increase with age (161).

Neurologic disorders

Intractable seizures – Although there has never been a controlled trial of IVIG for the treatment of severe, intractable seizures, a large number of anecdotal reports suggest that high doses of gammaglobulin are quite effective in reducing the frequency of seizures (307). Ariizumi et al. first tried to treat patients with refractory seizures in 1984 (308). They based their therapy on the observations in animals that some seizures could be autoimmune, often precipitated by viral encephalitis. Gammaglobulin was being used to treat other autoimmune diseases, so they attempted to treat 16 patients who failed conventional therapy. The 8 patients who had seizures for more than two years did not improve, but of the 8 with disease of shorter duration, 4 showed complete

remission, 2 had marked improvement and 2 had moderate improvement. Doses ranged from 100 to 200 mg/kg given several weeks apart. Interestingly, they found that a preparation consisting of intact IVIG was effective, but a pepsin-treated product was not (308). Their findings were confirmed in 8 additional patients with post-encephalitic seizures (309).

The immunologic basis for intractable seizures was further supported by the observation that many patients had IgG2 subclass deficiency. Twelve patients with refractory seizures were evaluated and 6 were found to have IgG2 deficiency and 5 had IgG4 deficiency, three of whom also had IgG2 deficiency (310). None had IgA deficiency. All were treated with 400 mg/kg of an intact IVIG preparation (Endobulin, Immuno, Austria) on Days 0, 15, and every 21 days thereafter. None of the non-IgG2 deficient patients responded, but 5 of 6 with IgG2 deficiency had a striking response with marked decrease in seizures and normalization of the EEG. Additional patients have been treated successfully (307), but there are no data, other than IgG2 subclass deficiency, that might indicate which patients might respond.

Autoimmune neuromuscular diseases – This heterogeneous group of disorders are all characterized by inflammatory changes in nerve or muscle that are related to the presence of circulating antibody or sensitized lymphocytes (311). Guillain-Barré syndrome (GBS) is a subset of the demyelinating polyneuropathies but patients usually recover spontaneously and it is distinct enough to be considered separately. All respond to immunosuppressive agents or plasmapheresis, but the morbidity of such therapy often is unacceptable. Therapy with IVIG may provide an alternative with fewer complications. The mechanism by which gammaglobulin might act to decrease disease activity is unknown, but there is evidence to support the presence of anti-idio-type antibodies that could compete with antibodies that recognize neuroblastoma cell lines (312, 313). Antibodies to neuroblastoma cells are present in up to 60% of patients with Guillain-Barré or chronic polyneuropathy. Binding of antibodies to the cell line were inhibited by IVIG or F(ab')₂ fragments of IVIG; the binding was similarly inhibited by F(ab')₂ fragments of IgG from a patient who had recovered from GBS (313). Recovery from GBS was associated with anti-idio-type antibodies recognizing a cross-reactive idio-type on anti-neuroblastoma cell line antibodies (312). Thus, it is possible, yet unproved, that IVIG naturally contains such anti-idio-type antibodies.

Guillain-Barré syndrome (GBS) – GBS is a subacute inflammatory demyelinating polyneuropathy

that leads to severe quadriparesis. About 20% require artificial respiration, 10 to 15% remain permanently disabled and 5% die of the disease. The pathologic features of GBS are similar to that of experimental allergic neuritis in animals. There is a lymphocytic infiltration of the myelin sheath which leads to segmental demyelination; there also may be the development of anti-peripheral nerve antibodies. Serum of patients with GBS can induce demyelination when injected into animals. Several studies showed that recovery is hastened by plasmapheresis, but the procedure is not widely available and has significant morbidity. IVIG was shown to be effective in polyneuropathy and other autoimmune diseases and so trials were started for treatment of GBS.

A pilot study of 8 patients using 400 mg/kg for 5 days was encouraging (314), with improvement in 6 of the patients. Three children treated during the acute phase of the illness responded rapidly and were able to sit within 24 h and two were able to walk within 48 h of initiating therapy (315). Based on these preliminary findings, a large, multicenter trial was conducted in the Netherlands comparing IVIG to "conventional" therapy with plasmapheresis (316). One hundred forty-seven patients were randomly assigned to exchange 200–250 cc/kg in 5 sessions or to receive 5 days of Gammagard at 400 mg/kg. In the plasma exchange group 34% of the patients improved by one or more functional grades compared to 53% in the IVIG group. The median time to improvement by one grade was 41 days with plasma exchange and 27 days with IVIG. There were fewer complications such as pneumonia, atelectasis, and thrombosis in the IVIG group, 39 compared with 68 in the plasma exchange group. There were no significant complications of the IVIG therapy.

Subsequent to the publication of this large study, two smaller studies were published that confirmed their results (317, 318). However, not all studies reported positive outcomes. Irani et al. at The Johns Hopkins Hospital reported 7 patients who had initial improvement but 5 relapsed within 1 to 16 days of treatment (319). Four subsequently improved with plasma exchange. They concluded that relapses were more frequent following IVIG than plasma exchange or no therapy. Similar concerns were raised in a report of 15 patients, seven of whom deteriorated within 5 days of initiating therapy (320). One remained ventilator-dependent for 2.5 months. One patient had a relapse 5 weeks after treatment, raising the question of whether the IVIG could adversely alter the natural history of the disease. No clear explanation of the conflicting results between the Dutch and the two American studies are forthcoming, but the poor responses raise a cautionary note

about the widespread use of IVIG until more controlled studies are performed.

Chronic inflammatory demyelinating polyneuropathy – CIDP can be considered the chronic form of Guillain-Barré syndrome. The benefit of plasma exchange and gammaglobulin in CIDP was shown as early as 1985 (321) and subsequently a number of anecdotal reports supported those early findings. A double-blind crossover study of patients who had an initial response to IVIG showed significant improvement when they were subsequently treated with IVIG compared to placebo (322), but these were selected patients and the role in newly diagnosed patients was unproved. In 1991, Cornblath et al. (323) reported subjective improvement in all 15 patients they treated with 300 to 400 mg/kg/day for 4 or 5 days, but only 3 had objective improvement in strength. Later that year the group in the Netherlands reported the results of an open study of 52 patients (324) treated with 2 g/kg of IVIG over 5 days. Thirty-two patients improved after therapy and the effect was sustained in 30 of those. Four patients improved one grade on the Rankin score, 10 improved two grades, 8 improved three grades, and 10 improved four grades. Twenty two required intermittent treatment to maintain the maximal level of improvement. Certain factors were associated with a favorable response: disease duration of less than 1 year, progression of weakness until approximately 4 weeks before onset of treatment, absence of discrepancy in weakness between arms and legs, areflexia of the arms, and slowed nerve conduction velocity of the median nerve. Patients fulfilling those criteria had a 93% probability of improvement. In contrast to these findings, a double blind, placebo controlled study by the same group did not show a difference in 15 patients randomly assigned to 2 g/kg of IVIG or placebo (325). Thus, despite very encouraging responses in uncontrolled studies, it appears that only a subset of patients respond and additional controlled studies are needed to determine the role of IVIG in CIDP, and, perhaps most importantly, to determine what criteria will allow proper selection of patients most likely to respond.

Multifocal motor neuropathy is associated with high levels of antibodies to ganglioside GM₁ or asialo-GM₁ (326). Improvement is often associated with a decrease in the concentration of the antibodies, suggesting that the antibodies are involved in the pathogenesis. A man with a three year history of multifocal motor neuropathy, but no anti-ganglioside antibody, was treated with 2 g/kg of IVIG and had one grade improvement in strength (327). A placebo infusion one month later had no effect. A second IVIG infusion resulted in another one grade improvement in strength. Five patients, four of

whom had increased levels of anti-asialo-GM₁ antibody, were treated with two monthly infusions of IVIG at 2 g/kg/dose (326). All patients with increased levels of antibody had consistent improvement within 3 to 10 days of therapy, though only one had sustained remission. In the other three improvement lasted only 20 to 30 days. The fifth patient with no anti-GM₁ antibody had no clinical or electrophysiological improvement. Chaudhry et al. at the Johns Hopkins University treated 9 patients in an open, uncontrolled trial (328). Patients had chronic progressive symptoms for 5 to 18 years with electrophysiologic evidence of multifocal demyelination and 7 had elevated serum titers of anti-GM₁ IgM antibody. They were treated with 1.6 to 2.4 g/kg over 3 to 5 days and strength improved in all patients within 3 to 10 days. Improvement peaked at 2 weeks and lasted an average of 2 months. Most patients responded similarly to repeated courses of IVIG. Interestingly, the titers of anti-GM₁ ganglioside did not decrease in any of the patients. As in the other inflammatory myopathies, the mechanism of action of IVIG is unknown and controlled studies are needed to carefully determine the role of gammaglobulin in decreasing the clinical, pathologic and electrophysiologic abnormalities.

Myasthenia gravis – Myasthenia gravis (MG) is an autoimmune neuromuscular disease caused by anti-acetylcholine receptor antibodies. It is characterized by progressive muscular weakness and severe cases have been treated with thymectomy, high doses of corticosteroids, and plasmapheresis to reduce the titers of anti-receptor antibodies. Gajdos et al. (329) treated five patients with grade III MG with 200 or 400 mg/kg of IVIG for 5 days. Neurological scores improved significantly in four patients and remained stable for 25 days. Antibody levels decreased but returned to pretreatment values by Day 25. Four additional patients were treated with a 7S IVIG, Intraglobin[®] and a pepsin-treated 5S IVIG, Gamma-Venin, in a crossover study (330). Antibody levels fell and symptom scores improved only during therapy with the 7S gammaglobulin. In a larger study, 12 patients were treated with 400 mg/kg of Sandoglobulin for 5 days (331). Eleven showed significant improvement beginning 3.6 days after the start of therapy. Vital capacity increased from 1748 ± 512 to 2700 ± 614 . These same authors reported further improvement with repeated courses of IVIG (332). In contrast to the previous studies, there was no decrease in the levels of anti-receptor antibody. Cook et al. reported a decrease in the total number of circulating lymphocytes during therapy of MG with IVIG, but the percentage of CD16+ and CD8+ cells increased and there was an increase in the number of IgG-specific Fc+ T cells which were thought to be

suppressor cells (333). Clinically IVIG appears to have a beneficial effect on muscular strength and decreases the need for corticosteroids, but it has not yet been tested in a controlled fashion which is necessary in a disease that shows marked fluctuations in severity.

Inflammatory myopathies – The inflammatory myopathies include dermatomyositis (DM), polymyositis (PM) and multifocal motor neuropathy. Both humoral and cell-mediated mechanisms are important in the pathogenesis of PM and DM (311). DM is primarily a humorally-mediated microangiopathy that leads to muscle ischemia or infarcts. The membranolytic attack complex C5b-C9 has been demonstrated in early lesions. The inflammatory infiltrate consists primarily of CD4+ T cells with lesser numbers of CD8+ T cells and B cells. In contrast, PM is primarily a T-cell mediated cytotoxic process in which muscle fibers are surrounded by cytotoxic CD8+ or $\gamma\delta$ T cells. The role of autoantibodies is not clear in either disease.

The primary therapy for inflammatory myopathies has been immunosuppression with corticosteroids and other drugs such as methotrexate, azathiaprine, or cytoxan, but although those drugs are often effective, they can be associated with significant morbidity and many patients are refractory (311). Plasma exchange and leukapheresis have been reported to be of benefit in DM and PM for several years, but in a controlled study of 39 patients, neither was any more effective than placebo despite reductions in muscle enzymes or leukocyte counts (334). Roifman et al. (335) first reported improvement of polymyositis following treatment of a 15-year-old girl who was wheelchair bound despite therapy with steroids, methotrexate, and cyclophosphamide. After 6 months of IVIG therapy given as 2 g/kg/month, she had significant improvement in proximal muscle strength from one to three grades. Twenty patients with DM or PM were treated with 4 monthly infusions of IVIG and 10 of 14 patients with PM and 5 of 6 patients with DM had a favorable response (336). All five patients with DM treated for up to 9 months had a favorable response (337). Treatment with IVIG was also beneficial in a single patient with scleroderatomyositis (338) and in a patient with polymyositis associated with chronic graft-versus-host disease (339). These case reports and small open studies are encouraging, but no controlled blinded studies have been conducted and in none of the trials have studies been done to evaluate the mechanism of action of the IVIG.

Multiple sclerosis (MS) – MS is a severe waxing and waning demyelinating disease of unknown etiology. There is considerable evidence that suggests an

autoimmune basis, with antibody and T cells directed against the axon sheath or the axons themselves. Conventional therapy consists of various immunosuppressive drugs, primarily corticosteroids. The success of IVIG in suppressing other autoimmune diseases stimulated Schuller & Govaerts (340) to treat 31 patients first with IM and later with IV gammaglobulin. Eleven patients improved and 9 remained stable, which was statistically better than a comparable group of 164 patients given conventional therapy. In another trial, 20 patients were given 5 g of IVIG every 2 months with only modest improvement (341), but the dose is much lower than usually used for immunomodulation. The mechanism by which IVIG might act, such as down-regulating B or T cells, is unknown, but it is of interest that monoclonal antibodies directed against T cells are effective (342), suggesting that control of T cell activity might be necessary. High doses of IVIG, 1600 mg/kg over two days, has been associated with a significant decrease in B, T, and NK cells (61). None of these or several anecdotal reports have been controlled studies; given the variable course of the disease, before the role of IVIG can be ascertained in MS, blinded studies will be required, probably using higher doses than in the previous trials.

Miscellaneous neurologic disorders – The use of IVIG has been reported anecdotally in a variety of other neurologic disorders, but data are inadequate to determine whether the treatment is efficacious. Four patients with inclusion body myositis and progressive weakness were treated with IVIG at 2 g/kg/month for two months (343). Typically, this disease is progressive and poorly responsive to immunosuppressive agents. However, with IVIG three of the four had improvement or normalized their muscle strength. A single patient with adrenoleukodystrophy improved after low-dose therapy with IVIG (344). A patient with another disorder that is usually progressive and poorly responsive to immunosuppressive therapy, paraneoplastic cerebellar degeneration, showed complete recovery after therapy with 2 g/kg infused over 5 days (345). The patient had failed plasmapheresis but did not have a decline in levels of anti-neuronal antibodies. IVIG was also of benefit in 14 patients with HTLV-1-associated myelopathy (346). The best response occurred in the patients with the highest levels of anti-HTLV-1 antibody in the CSF.

Collagen-vascular disease

Systemic lupus erythematosus (SLE) – One of the most common and potentially the most severe of the autoimmune diseases, SLE can affect nearly every organ. Nephritis is associated with a particularly

poor prognosis. Standard therapy includes high dose corticosteroids, but many patients are refractory or can not tolerate the side effects so other immunosuppressive agents are required. Several immune abnormalities occur in SLE (347), including polyclonal B cell activation with production of autoantibodies, especially anti-DNA antibody which is the most characteristic of the disease. In addition, T cell abnormalities have been identified, especially suppressor T cell dysfunction and abnormal mitogen and antigen responses, and patients have poorly characterized dysfunction of macrophages and neutrophils. Based on the success of IVIG in other autoimmune disorders such as ITP, it has been used in several small studies for patients with SLE. Gaedick et al. (348) reported the use of IVIG in two patients in 1984, one of whom responded. Others reported improvement in vasculitis and, in one patient, encephalitis, with high doses of IVIG in uncontrolled trials involving only a few patients (349–353). One possible complication of the use of IVIG in SLE patients may be worsening of renal function in some patients with nephritis (350, 352). Recently, two patients with life-threatening complications of SLE that were refractory to corticosteroids and immunosuppressive drugs were treated with 2 g/kg of Sandoglobin® over five days (354). The first patient, a 21-year-old woman with severe pneumonitis that necessitated mechanical ventilation, had slow improvement, though she still required high doses of corticosteroids. She had worsening of her disease after discharge so monthly infusions of IVIG were begun and she remained in remission on 5 mg of prednisone per day. A second patient had severe lupus nephritis and developed pneumonia secondary to the cyclophosphamide therapy necessary to control her renal disease. She was treated with 2 g/kg of IVIG and had a prompt and dramatic improvement in clinical status and renal function. Infusions of IVIG were continued monthly and she did well except for a flare of her nephritis 10 months later that responded to a pulse of prednisolone and cyclophosphamide. As with the other collagen vascular diseases, there have not been any controlled studies in SLE and therefore the role of IVIG can not be determined with any certainty.

Lupus anticoagulant – Antiphospholipid antibodies (aPL), which include lupus anticoagulant (LA) and anticardiolipin antibodies (ACA), are associated with a variety of hematologic and autoimmune diseases such as autoimmune thrombocytopenia and hemolytic anemia and lymphoproliferative disease. The occurrence of these antibodies has been associated with recurrent abortions as well as eclampsia and thrombotic episodes in pregnant women. Infusions of IVIG were shown to be transiently effective

tive in a patient with ITP associated with LA (355) and were used in a few patients with spontaneous abortions (356–358). One large, but uncontrolled, study included 20 women with a history of recurrent abortions treated with 500 to 600 mg/kg of IVIG per month beginning in the fifth week of gestation (359). At the time of publication 11 had delivered healthy babies, 5 were still pregnant, 1 had an ectopic pregnancy, and only 3 had suffered an abortion, for a success rate of 82 to 86%. In the most recent study (360) three women with LA and ACA and a history of recurrent abortions were treated with high doses of Sandoglobulin®. The first patient was treated with 1 g/kg every 4 weeks beginning in the 18th week of pregnancy and delivered a normal term infant. She had a subsequent pregnancy and delivered a normal infant after only two infusions of IVIG. The second patient began infusions of 1 g/kg every 4–5 weeks in the eighth week of gestation. In the 24th week aspirin and labetalol were started because of hypertension. She developed preeclampsia but delivered a normal infant by cesarean section in the 34th week of gestation. The third woman had a history of four first trimester abortions; she began monthly infusions in the tenth week and delivered a 2650 g infant at 36 weeks. In all three women they noted a decrease in the titer of LA and ACA. Normal human gammaglobulin is able to neutralize LA activity *in vitro* (361, 362), suggesting that there may be an anti-idiotypic antibody in IVIG. However, although Galli et al. (363) were also able to demonstrate neutralization *in vitro*, they felt that the time course of the effect of IVIG *in vivo* was inconsistent with an idiotypic-anti-idiotypic interaction and felt that another mechanism must be operating. Thus far, the mechanism has not been defined and no controlled studies have been done for any of the disorders associated with LA or ACA.

Systemic vasculitis – Systemic vasculitis is often associated with the presence of anti-neutrophil cytoplasm autoantibodies (ANCA), though the pathogenic role of the antibodies is not proven. There is an association of ANCA titers and disease activity and also an association of certain antibodies with particular diseases, such as anti-proteinase 3 with Wegener's granulomatosis. *In vitro*, ANCA alters neutrophil function and promotes cellular-dependent endothelial cytotoxicity. However, ANCA may still be present during remission, and other abnormalities of B and T cell function have been described. Seven patients were treated in an open study with 2 g/kg of IVIG over five days (364). Five had progressive disease despite immunosuppressive therapy and two were newly diagnosed. All had clinical improvement that was sustained in six. There was a transient rise in ANCA titers followed by a decline to 51% of

pretreatment values. There were no adverse effects. A subsequent study of 16 patients reported immediate benefits in 15 and sustained remission in eight (365). They were able to demonstrate the presence of anti-idiotypic antibodies to ANCA in IVIG that were able to block the binding of the autoantibody *in vitro* (365). The importance of this *in vitro* observation to the effects *in vivo* are not known. No controlled or multicenter studies have been done. Infusions of IVIG were used successfully to treat another form of vasculitis, Churg-Strauss syndrome, in which ANCA are not involved (366).

Rheumatoid arthritis (RA) – Rheumatoid arthritis is a systemic disease but the primary manifestation is inflammation of the synovial tissues. Some patients have IgM anti-IgG "rheumatoid factor" in their serum, the presence of which signifies a high risk of erosion of the articular cartilage. The presence of antibody is less common in children with RA and is not necessary for inflammation of the joint as indicated by the high incidence of arthritis in patients with X-linked and common variable hypogammaglobulinemia. Activated CD4+ and CD8+ T cells have been identified in synovial tissue and fluid, suggesting a possible role for cell-mediated immune destruction.

In 1982, Sany et al. reported a favorable response to infusions of gammaglobulin eluted from placentas in 7 of 11 patients hospitalized with severe RA (367). They noted an increase in "active" E rosettes and mitogen responses, but both the clinical response and the immunologic changes were short lived. A much larger trial involving 31 patients was conducted by Combe et al, comparing Veinoglobuline (Institut Mérieux, Lyon France), an intravenous gammaglobulin preparation derived from placental blood, with a preparation of IgG eluted from placental tissue (368). The patients were divided into seven groups, so there were only a few patients in each group. The maximum dose was 3.5 g/day for three days each month, and the largest group of 12 patients received 1.5 mg/day of placenta-eluted IgG for seven days each month. The best response occurred in this group, and, as in the previous study, they noted an increase in the number of active E rosettes and a decline in Fc receptor-bearing lymphocytes. While they attributed the effect to the use of IgG eluted from placental tissue, which might contain unique antibodies such as anti-HLA-DR (368, 369), the groups were too small and the doses of IgG used were far lower than the high dose therapy used in most studies. It is interesting that both these studies used blood derived from placentas, and there have not been any studies done using standard IVIG preparations. However, it is known that the arthritis associated with immune deficiency may improve with

therapy with IVIG (370, 371), and recently arthritis in a patient with acquired hemophilia improved when she was treated with IVIG (372). Therapy with IVIG was also shown to decrease the symptoms of systemic juvenile RA (373). In this study eight patients were infused with 1 g/kg on two day per month for 6 to 13 months. There was significant improvement in the arthritis in 5 of the patients and in the extraarticular symptoms in seven. Prednisone requirements decreased 80%. These studies are suggestive but multicenter controlled studies are needed and certainly are justified in this disease that causes such great morbidity.

Inflammatory bowel disease (IBD) – The etiology of IBD is thought to be autoimmune or associated with infection. It often occurs as an isolated problem or may be associated with arthritis or immune deficiency. The inflammation may involve only the large or the small bowel, or both. Crohn's disease can involve large or small bowel and differs histologically from ulcerative colitis.

There have been a few anecdotal reports of beneficial results of IVIG in IBD but no controlled studies. The only extensive study was that of Levine et al. at the University of Washington (299). They studied 12 patients with moderate to severe disease who either failed corticosteroid therapy or were reluctant to try immunosuppressive drugs. They were treated with 2 g/kg over 2 or 5 days and then received 200–500 mg/kg every 2 weeks for 12 or 24 weeks. Six patients completed the trial and 5 had a good clinical response and in 4 they demonstrated decreased inflammation on biopsy. Prednisone doses were reduced from 41.7 ± 8.0 to 1.9 ± 1.2 . Six patients failed to complete the full study, four did not have a prompt response and elected to have a colectomy and two required surgical intervention early in the course of therapy. This was not a blinded study, but the results are sufficiently encouraging to justify controlled trials involving a larger number of patients.

Kawasaki disease (KD)

Clinical and immunologic features – Kawasaki disease is an acute self-limiting febrile illness that primarily affects infants and children (374, 375). It was first reported in 1967 by Kawasaki who termed it acute febrile mucocutaneous lymph node syndrome. Diagnostic criteria include fever for at least five days, bilateral conjunctivitis, cervical lymphadenopathy, changes in the oral mucosa ("strawberry tongue"), erythematous rash, and swelling of the distal extremities followed by desquamation. Laboratory findings include thrombocytosis, elevated erythrocyte sedimentation rate, leukocyte count

$> 20,000/\text{mm}^3$, and presence of circulating immune complexes. The prominent pathologic feature is vasculitis of the small-to-medium arteries throughout the body, but particularly in the coronary arteries. Complications are common in untreated patients, including coronary artery aneurysms, myocarditis, myocardial infarction, arthritis, meningitis, sterile urethritis, and hydrops of the gallbladder.

The highest incidence is in Japan where more than 104,000 cases have been reported (374). It has become one of the leading causes of acquired cardiac disease. In Japan the mortality rate among boys is markedly increased, but only during the first two months after diagnosis (376). The disease often occurs in epidemics, with peak incidence in the Spring and Fall, leading to speculation that it is an infectious disease. Several infectious agents have been implicated, including yersiniae, rotavirus, retroviruses, Epstein-Barr virus, *leptospirae*, and *propionibacteria*. One prominent theory is that Kawasaki disease is caused by immune complexes with house dust mites. Other associated factors have been investigated including exposure to rug shampoo, living near a body of water, and mercury intoxication (375). Thus far, no relationship has been proven. Current theories center on genetic predisposition to an infectious agent that can act as a "superantigen" (374).

The acute phase of Kawasaki disease is characterized by immune activation. There is an increased percentage of CD4+ activated T cells, selective expansion of $V_{\beta}2+$ and $V_{\beta}8+$ T cells, deficiency of CD8+ suppressor T cells, increased serum levels of soluble CD25, CD4, and CD8, polyclonal B cell activation, increased cytokine production, particularly interferon, IL-1, TNF- α , and IL-6, and antibodies to vascular endothelial cell antigens and neutrophil cytoplasmic antigens (374). As a result of the cytokine production, there is increased expression of ICAM on endothelial cells. In a mouse model of coronary arteritis induced by *Lactobacillus casei*, destruction of the endothelium could be blocked by antibodies to TNF- α which decreased ICAM-1 expression and adherence of neutrophils to endothelium (377). The global stimulation of the immune system and the selective expression of a few T cell receptors is characteristic of bacterial antigens that can act as superantigens. Streptococcal pyrogenic exotoxin type B selectively stimulates $V_{\beta}2$ and $V_{\beta}8.1$ expression, further supporting the enticing possibility that Kawasaki disease is caused by an abnormal response to a streptococcal toxin.

Therapy with IVIG – Aspirin has been used for KD since 1977 for its anti-inflammatory, antipyretic, and antiplatelet effects. It also reduced the incidence of cardiovascular complications, but coronary artery

aneurysms remained a significant problem. In 1984 Furusho et al. reported a multicenter study of 95 patients treated with aspirin alone or aspirin in combination with five days of a sulfonated IVIG (Venilon) at 400 mg/kg/day (378). He theorized that the inflammation in KD was similar to the immunologic changes in ITP and, therefore, used IVIG as an immunomodulating agent in the same doses used for ITP. Within 29 days of the onset of the disease coronary artery lesions developed in 42% of the aspirin group but only 15% of the IVIG group. The study was criticized because it was not blinded and the incidence of coronary lesions was unusually high. Nonetheless, the data were so striking that numerous other studies followed (374, 375). Reducing the period of treatment to 3 days was less effective than the initial 5 days, though there were fewer aneurysms compared to aspirin alone (379). Lower doses of only 100 mg/kg/day were clearly less effective (380).

A similar, but blind, multicenter study was conducted in the US. and reported by Newburger et al. in 1986 (380). Patients were randomized to either aspirin alone or aspirin plus 400 mg/kg of IVIG for 5 days. The echocardiographer did not know which patients received IVIG. The IVIG used was ImmunoAG (Vienna, Austria) prepared using plasma from US. donors. If KD is an infectious disease with a higher incidence in Japan, it might be expected that the levels of the appropriate antibody might be higher in Japanese donors. Despite these concerns, the results were similar to those of the Japanese investigators. At two weeks after illness there were aneurysms in 23% of the aspirin group compared to 8% in the gammaglobulin group. Five weeks later aneurysms persisted in 18% of the aspirin group compared to 4% in the IVIG group. Even though the incidence of aneurysms detectable by echocardiography decreased over time, there was pathologic evidence on a few patients that indicated that once an abnormality was detected the artery might never be normal and could predispose the patient to cardiovascular disease later in life (381). Thus, the American Board of Pediatrics, the Canadian Pediatric Society, and the FDA and CDC jointly recommended that IVIG be used in the treatment of Kawasaki disease as long as strict criteria were used to make the diagnosis (382). Subsequent studies indicated that a single dose of 1 g/kg (383) or two doses of 1 g/kg (384) were as effective as 5 days of 400 mg/kg/day. Indeed, the patients treated with 1 g/kg had more rapid resolution of fever and were discharged from the hospital one day earlier (385).

The mechanism of action of IVIG in KD is not known. Patients treated with IVIG demonstrate a rapid resolution of fever and normalization of laboratory values. Immune complexes are not reduced

(386), but there is a rapid decrease in the number of activated T cells and spontaneous B cell activation, and an increase in suppressor T cells (387). Subsequent studies by Leung and his colleagues demonstrated decrease in IL-1 and TNF, and subsequently showed evidence of decreased endothelial cell activation (388, 389). Cytopathic IgM antibodies directed against activated endothelial cells (390) were not reduced by IVIG therapy (389).

The use of IVIG for the treatment of Kawasaki disease is well established (382, 391). It was recently shown to be cost effective, especially in a one day dose schedule, because of the reduced cost of treating coronary artery disease. If KD leads to additional disease later in life the cost benefit may be much higher. Nonetheless, IVIG is expensive and has been associated with side effects. It is important to confirm the diagnosis (382, 391) and to begin therapy early in the course of the disease. Ultimately it may be possible to identify patients who are at high risk of developing aneurysms and treat only that subgroup. Identification of the cause may also allow the use of more specific therapy such as monoclonal antibodies directed against a specific toxin.

Miscellaneous inflammatory and autoimmune disorders

Asthma – In recent years physicians have rediscovered the inflammatory nature of asthma. Although bronchospasm is a conspicuous feature of asthma, the pathogenesis lies in the inflammatory changes in the mucosa and submucosa (392). Activated T lymphocytes are found in the serum, in biopsies of bronchial mucosa, and in BAL fluid (393, 394). A number of proinflammatory cytokines are increased in acute asthma (395), and recent studies also indicate that ICAM receptors are up-regulated on respiratory epithelium (396), suggesting a mechanism by which the epithelial cells can be targeted by activated T cells and macrophages. Asthma has been shown to be responsive to immunosuppressive agents, especially corticosteroids, but also others such as methotrexate or gold. Some severe, steroid-dependent asthmatic patients may have IgG subclass deficiency that could predispose them to respiratory infections (90, 94, 397–399), but even in patients treated for long periods with high doses of corticosteroids, immune deficiency is uncommon (400). Smith (397) proposed the use of IVIG to treat patients with IgG subclass deficiency and recurrent infections to reduce the incidence of the infections that could exacerbate their asthma. Several investigators reported a decrease in asthma and recurrent respiratory infections when patients were treated with intravenous or intramuscular gammaglobulin (75, 93, 401, 402). Although in these small un-

controlled studies there was a decrease in the severity of asthma, it is not clear whether the improvement was due to the decrease in the incidence of infections or to an immunomodulatory effect of the IVIG. Mazer & Gelfand treated eight severe steroid-dependent asthmatic children in an open-label trial of IVIG (403). Patients were infused with 2 g/kg over a two-day period every month for seven months. They were evaluated by symptom scores, skin test reactivity, steroid dose, and need for additional medications. Symptom scores decreased for seven of the eight patients to approximately 50% of baseline. The eighth patient had low scores prior to the study. Steroid use decreased from a mean alternate day dose of 32.5 mg to 11.5 mg. One of the more interesting observations was that the immediate hypersensitivity skin test reactivity to common allergens decreased during the period of therapy, suggesting an immunomodulating effect of the gammaglobulin. Since this was an unblinded study, some of the improvement could be subjective, and double-blind, placebo-controlled studies will be required to determine the effectiveness of IVIG in this common disease; even then, strict criteria will have to be developed to determine when such expensive therapy can be justified.

Diabetes mellitus – Autoantibodies directed against islet cells have been identified and are thought to be involved in the pathogenesis of type I diabetes mellitus (404). Infiltrates of T lymphocytes in islet cells provide further evidence of autoimmune disease. Six children with recently diagnosed diabetes were treated with 400 mg/kg of IVIG per day for five days and then once per week for 6 months. All showed a return to normal of glycosylated hemoglobin and five of the six had a partial remission of 15 to 30 months (405). This was in contrast to a mean remission of 6.8 months in 48 diabetics treated with insulin only. A larger, controlled study of 20 newly diagnosed patients also supported a role of IVIG in treating newly diagnosed patients (406). Patients were treated using the same schedule as the previous study and the children had decreased insulin requirements for the duration of the study, but the differences were no longer seen after one year. Despite these results, the effect of IVIG on patients with long-standing disease and the long-term benefits of therapy have not yet been determined.

Bullous pemphigoid – Bullous pemphigoid is a severe blistering dermatitis characterized by linear deposits of IgG along the basement membrane and often associated with circulating anti-epidermal cell antibodies. This disease, which can be fatal, is usually treated with steroids, immunosuppressive drugs, or plasmapheresis. The only reported trial of IVIG in

pemphigoid was that of Godard et al. (407) who treated 9 patients with 400 mg/kg, one with 300 mg/kg, and another with 100 mg/kg per day for five days. Eight of the patients on the high dose regimen showed dramatic and rapid improvement that lasted approximately two weeks. Three of the patients were given a second course of IVIG with a similar effect. There was no effect on the deposition of anti-basement membrane antibody and no patient had a sustained remission. The authors did feel, however, that the use of IVIG might have a steroid-sparing effect.

Adverse reactions to intravenous gammaglobulin

Acute "phlogistic" reactions

Acute reactions to infusions of gammaglobulin have been recognized for more than 50 years and have been well summarized by Barandun & Isliker (6). The initial concentrates of gammaglobulin, whether prepared by Cohn fractionation or other techniques such as ammonium sulfate precipitation, were intended for intramuscular use. However, injections were painful and the amount that could be injected was limited. Thus, in 1945 Cohn used IgG from his laboratory and infused it into normal volunteers. Doses of 25 to 50 ml were well tolerated by healthy adults and by normal children with acute infections. It was assumed that it was safe to administer the IgG intravenously until the late 1940s when Janeway et al. (1) tried to alter the course of severe measles infection by infusions of large doses of gammaglobulin. Each infusion led to life-threatening reactions with hyperpyrexia, vasomotor collapse, convulsions, and respiratory compromise. The reason for these catastrophic reactions was unknown and largely unexplored for more than a decade until the need to treat patients with immune deficiency with larger doses of gammaglobulin stimulated the investigators at the Swiss Red Cross to examine the problem.

A group led by Barandun, Kistler, Isliker and others used the intramuscular IgG prepared by the Swiss Red Cross by the Kistler-Nitschmann modification of the Cohn fractionation. They diluted the 16% solution 10-fold and infused it slowly into normal volunteers without adverse effect. However, infusion of only a few drops of the solution into a patient with hypogammaglobulinemia provoked severe vasomotor collapse with dyspnea, back pain, vomiting and diarrhea, and later fever and chills. After further uneventful infusions into healthy subjects they systematically tested the preparation in 15 patients with hypogammaglobulinemia and 55 patients with normal or elevated immunoglobulins (53). The results were revealing. Forty-eight of the normal patients tolerated a slow infusion of 110 ml of a 1.45% solution, but 14 of 15 of the hypogammaglobulinemic patients experienced early signs of

flushing, oppression, nausea, and shivering, followed by a rise in temperature to 38° or 39°C. Two of the patients suffered more severe, anaphylactoid reactions. Whenever an adverse reaction occurred the infusion was interrupted until the symptoms resolved, and then, somewhat surprisingly, the remainder of the infusion could be completed without incident. If a minimum dose of 1.5 to 3 g was infused, the patient would be "desensitized". There obviously were factors in the immune deficient patients that predisposed them to intolerance, which they termed the "endogenous factors", but since patients tolerated IgG in the form of plasma, there must be "exogenous factors" in the IgG preparation itself that lead to adverse reactions.

In evaluating the exogenous causes of reactions, they theorized that the IgG was spontaneously fixing complement. They were able to demonstrate that IgG concentrates contained aggregates that could fix complement, and when they ultracentrifuged the IgG, the fractions containing the larger aggregates were the most anticomplementary and caused the most severe reactions. Since centrifugation was not a practical method to rid the IgG of aggregates, they explored other methods such as enzyme digestion, modification of the Fc portion of the IgG molecule, and treatment at low pH. These experiments led to the development of the product prepared at low pH with a trace of pepsin and now marketed as Sandoglobulin®. Other manufactures have used other techniques to reduce aggregation, as was discussed in the section on IVIG products. Despite chemical modification, many of the early products caused significant reactions until it was discovered that the addition of a sugar such as maltose would prevent re-aggregation and significantly increase patient acceptability (30). Some of the early preparations were contaminated with kinins, prekallikrein activator or proteolytic enzymes, but the currently available preparations are all tested and must be free of these contaminants. The IVIG preparations today are all free of multimers of IgG and do not spontaneously fix complement. They are generally well tolerated in the majority of patients, but, as discussed below, hypogammaglobulinemic patients are still at risk of adverse reactions because of their "endogenous factors".

Understanding of the role of aggregates in the gammaglobulin still did not explain why agammaglobulinemic patients differed so markedly from those with normal gammaglobulin levels. Though the explanation is far from proven, it is thought that patients differ in at least two ways. First, they lack the IgG that normally is bound to the Fc receptors on monocytes, macrophages, and other phagocytic cells. Interaction of the cells through their Fc receptors activates them and causes them to release cyto-

kines and chemical mediators. Once these Fc receptors are "saturated" with IgG, the cells no longer become activated. If the IgG is infused slowly, or the infusion is interrupted until the reaction subsides, then no further reaction occurs. This is supported by their observations that only 7 S, intact IgG, but not 5 S fragments without an intact Fc portion, was capable of desensitizing patients to subsequent infusions of IgG.

Secondly, they suffer from chronic infections and therefore, have a large load of antigen that will then bind to the antibodies as they are infused. This helps explain why reactions are more common and severe during the initial infusions and during periods of infection. This was true even of some normal patients during severe infections such as those early patients treated for severe measles.

Anaphylactic reactions

The reactions described in the previous section are relatively common and seldom severe or life-threatening. In contrast, a few patients have been described who have had life-threatening anaphylactic reactions after infusion of only a few milliliters of IVIG. Two patients with CVID and undetectable levels of IgA had IgE anti-IgA antibodies that increased in titer after an adverse reaction and decreased when they were infused with Gammagard that had very low levels of IgA (0.6 mg/dl) (99). Subsequently, other similar patients have been studied, and the relationship of the level of IgE anti-IgA to the severity of the reaction was quite good. In contrast, others have reported patients with IgG anti-IgA in whom there was not a good correlation between the presence of anti-IgA and adverse reactions (408). They also identified one patient who had transient levels of IgE anti-IgA but that patient did not suffer any adverse effects when infused with Endoglobulin (Immuno, SA, IgA content 0.005 to 0.05 mg/m).

Anti-IgA antibodies are commonly found in patients with immune deficiency who are treated with intramuscular or intravenous gammaglobulin (408, 409). Sera from 305 patients with immunoglobulin deficiencies were evaluated for anti-IgA antibodies using indirect agglutination and ELISA (409). Anti-IgA antibodies were detected in 22% of patients with hypogammaglobulinemia and 29% of patients with selective IgA deficiency. All had IgA concentrations <0.05 g/L. Most antibodies were of the IgG class, and no IgE antibodies could be detected with the methods used. Seven of eight patients with anti-IgA antibodies tolerated infusions of IVIG that was low in IgA, but the eighth experienced a near-fatal reaction at the seventh infusion.

The association of anaphylactic reactions to blood products and anti-IgA antibodies was reported more than 20 years ago. Six patients with serious reactions to blood, plasma or ISG were found to have IgG antibodies against IgA (410). Those with a history of anaphylactic reactions had antibody of broad specificity, whereas those who were multi-transfused and had a history of urticaria and anaphylactoid symptoms had antibody of limited specificity. The role of these antibodies in causing anaphylactic reactions was questioned by Rivat et al. who studied 84 patients who had experienced transfusion reactions and 1010 healthy blood donors (411). They found equivalent percentages and titers of IgG anti-IgA antibodies in both groups. All of the antibodies were of limited specificity, as indicated by their reaction to only one or two of the IgA myeloma proteins used in the assay. Thus, although anti-IgA antibodies directed against class, subclass, or allotype may be of clinical importance, antibodies of limited specificity may be an incidental finding. These observations were supported by the studies of Ropars et al. (412) who concluded that only the class-specific anti-IgA antibodies were of importance and that the majority of reactions were due to anti-complementary effects of the gammaglobulin preparations. Elevated titers of IgE anti-IgA were also detected in patients given multiple injections of gammaglobulin, but as with the IgG anti-IgA antibodies, they were of limited specificity and not associated with adverse reactions (413). Only those with antibodies of broad specificity demonstrated an association with intolerance reactions.

It is clear that the majority of adverse reactions to IVIG and other blood products are caused by anti-complementary effects of the gammaglobulin, whether induced by aggregates of IgG or by antigen-antibody complexes. However, patients with IgA levels <0.05 g/L are at significant risk of developing class or subclass specific IgG or IgE anti-IgA antibodies, and these antibodies, which are of broad specificity, can induce serious, potentially fatal, reactions when they are infused with IgA-containing IVIG. Gammaglobulin products such as Gammagard®, which contain very low quantities of IgA, should be considered for such patients. The role and importance of monitoring IgE anti-IgA titers has not yet been clearly established but may be helpful in predicting the risk of serious reactions.

Transmission of viral infections

The risk of transmitting viral infections through blood products was a concern of blood banks and pharmaceutical companies long before the identification of the AIDS virus. The transmission of hepatitis B was greatly reduced by testing plasma, but

non-A, non-B hepatitis (now known as hepatitis C) could not be detected until recently and continued to be a significant problem. HTLV-1 was transmitted through blood transfusions and some blood products such as cryoglobulin and Factor VIII; fortunately, it has not been transmitted by blood products that have undergone Cohn fractionation since, fortuitously, ethanol inactivates the virus. Nonetheless, studies are underway to find more effective methods to inactivate all viruses.

Hepatitis – Hepatitis B has not been a significant problem in preparations of gammaglobulin. The virus is not completely inactivated but appears to be partitioned in the early fractions. If the contamination is very heavy it is possible for some virus to be detected in the final product, as was evidenced in scattered reports in the US. before 1975 (414) and an outbreak in India (415). A study of blood products prepared between 1957 and 1972, before widespread screening was available, demonstrated that 40% of Factor IX concentrate, 20% of albumin and 0.7% of immune serum globulin lots were HBsAg positive (416). Since the requirement for testing of the plasma source by sensitive techniques, there has not been a reported case of transmission of hepatitis B in Europe, Japan, or the US.

Unfortunately, the story for non-A, non-B hepatitis (NANBH) is not as reassuring. In 1984 Lever and his colleagues reported elevated transaminases in 12 patients with primary hypogammaglobulinemia who had been treated with an IVIG preparation made from Cohn-fractionated plasma (417). Most of the patients were asymptomatic, but 10 months later 10 still had elevated enzymes and pathology on the three that were biopsied showed severe lobar hepatitis with a prominent cellular infiltrate. Upon follow-up two years later, half had signs of progressive liver disease (418). In 1985, investigators in Seattle reported elevated ALT and AST in 7 of 16 patients given a new IVIG product prepared by ion-exchange chromatography; one patient developed frank hepatitis (419). The most concerning evidence of transmission of NANBH is that of the Swedish investigators who reported clinically significant hepatitis in 16 of 77 patients treated in the US. and Sweden with a Swedish IVIG preparation Gammonativ (Kabi Vitrum, Stockholm) prepared by ion-exchange chromatography from Cohn-fractionated plasma (420). All 16 had aminotransferases at least 2.5 times normal; five had signs of severe liver disease including ascites and edema. Five patients died and in four liver disease was a major factor. It is of interest that many patients had received intramuscular gammaglobulin from the same plasma source without developing hepatitis. It was possible to transfer hepatitis into chimpanzees when they were inoculated with sera

from five patients. Most recently, Williams et al. in Edinburgh, Scotland reported NANBH in 4 of 34 immune deficient patients treated with IVIG prepared by the Scotland Blood Transfusion Center by pH4/mild pepsin treatment (421). One developed chronic NANBH proven by biopsy, but the other 3 recovered fully. Several patients with NANBH have been treated with α -interferon with good response (422, 423).

Despite these reports of NANBH, until recently the overall safety profile of IVIG had been quite good; millions of grams of gammaglobulin had been infused without difficulty. A retrospective analysis of 41 patients treated with IVIG for 6 to 15 months found no evidence of hepatitis (424). Another review of 64 patients treated for ITP showed no evidence of HIV or abnormal liver function (425). However, in late February 1994 there were multiple reports of elevated transaminases related to infusion of several lots of Gammagard®. Nine patients were reported in Madrid and Seville, five patients in Sweden, and two cases were reported in the US. Several of the patients were positive for hepatitis C by the PCR technique, but the data are still preliminary and most of the patients have not been tested. Based on these reports Baxter withdrew all lots of Gammagard® worldwide. Subsequent to the initial reports there have been several other cases identified in the US and undoubtedly others will be reported as patients are screened for evidence of transaminase elevation. Thus far all cases have been related to the use of Gammagard®; other preparations utilize various procedures, discussed in a later section, to further reduce the risk of viral transmission. Gammagard® will be replaced with a detergent-treated preparation, Gammagard®-SD, in the near future. However, no process can be considered to be absolutely reliable. Prior to the development of a sensitive test for hepatitis C, lots of plasma were screened to eliminate those with elevated ALT/AST to eliminate donors most likely to be viremic. It was hoped that the addition of testing for antibody to hepatitis C would provide an even greater margin of safety, though there was concern that eliminating antibody would reduce the ability of the gammaglobulin to neutralize any virus that should escape detection. It is possible that this was a factor in the recent outbreak of hepatitis C, but it will be months before all of the data can be collected and analysed.

HIV infection – Hundreds of patients were treated with IVIG prepared from plasma obtained from HIV positive donors. Prior to the institution of testing of donors, most lots of IVIG contained antibody to HIV, at least by ELISA (426, 427), yet despite the well documented transmission of HIV by plasma, cryoglobulin, and Factors VIII and IX, there has

never been documented transmission of AIDS by any IVIG preparation. Testing by the more specific Western blot was negative for most lots of gammaglobulin (426–428), raising the question of specificity. Follow-up of immunocompetent patients given IVIG indicated no evidence of seroconversion, though some were antibody positive immediately after infusion of antibody-positive IVIG (428, 429). Webster reported the presence of reverse transcriptase and retroviral RNA in two patients with agammaglobulinemia who had been treated with IVIG (430), though the association with the gammaglobulin therapy could not be demonstrated. Prince et al. at the New York Blood Center suggested that it might be possible for the HIV to survive the Cohn fractionation process (431), though they did not indicate that HIV had been transmitted by any preparation. However, extensive testing of plasma spiked with large quantities of HTLV-III indicated that the infectivity during Cohn fractionation could be reduced from $>10^6$ to $<10^0$ infectious units; the ratio of the reduction was $1:10^{-15}$ (432, 433).

Treatment of IVIG to reduce the risk of virus transmission – The Cohn-Oncley fractionation technique greatly reduces the risk of viral transmission, but as indicated by the discussion of NANBH, it is possible for some viruses to survive the process. Several approaches have been used to further reduce the possibility of transmitting a viral infection (434). Stephan at the Biotest Serum Institute (435) introduced an inactivation step using β -propiolactone which is effective against most viruses. The IVIG preparation, marketed in Europe as Intraglobin®, appears to be effective clinically though *in vitro* testing suggests that the Fc activity of the molecule is reduced. The studies of Hamamoto et al. in Japan indicated that HIV, hepatitis B, vesicular stomatitis and Sindbis viruses were effectively eliminated from IVIG by a combination of Cohn fractionation and polyethylene glycol (436). However, since this is the same technique that was used to produce products that have been demonstrated to transmit NANBH, as was discussed in the section above, some care must be used in interpreting their results. Subsequently they added a heat inactivation step at 60° for one hour to further improve viral elimination (437).

The New York Blood Bank has pioneered development of detergent inactivation of viruses which is effective against most lipid-enveloped viruses. Initially, a Tween 80/ether mixture was used, but the ether is highly flammable and the Tween difficult to remove from the final product. A combination of tri(n-butyl)phosphate and sodium cholate very effectively inactivates HIV, NANB, and hepatitis B (438). When plasma that was intentionally spiked with virus was treated with this mixture no virus could be

detected and infection did not occur when the plasma was inoculated into chimpanzees (439, 440). The viruses of greatest concern, HIV, hepatitis C, and hepatitis B, are all lipid-enveloped viruses and are therefore susceptible to detergent inactivation. Other NANB viruses have been described that are not enveloped, and parvovirus, which has been transmitted by blood transfusions, also is not enveloped. Thus, these viruses may not be susceptible to detergent treatment. Ultraviolet light was shown to be able to inactivate a variety of single stranded RNA and double-stranded DNA viruses (441) without damaging IVIG or albumin. Previous reports of the failure of UV light to inactivate hepatitis virus may have been due to poor control of the process (434, 441). UV light may be useful in combination with detergent treatment. The New York Blood Center has licensed its detergent process to several pharmaceutical companies for use with a variety of blood products. Concerns still remain, however, that although the virus may be disrupted the nucleic acid may continue to be infectious. Further studies are needed before the ideal process is available.

Other adverse reactions

Increased risk of infection – Concerns about IVIG increasing the risk of infection are mostly theoretical. They are based on the assumption that the mechanism of action of IVIG in autoimmune disease is paralysis of the reticuloendothelial system. If that were true, then it would be possible to inhibit phagocytosis of bacteria or fungi and increase the risk of sepsis. Few studies are available to provide data on this question. Kim et al. reported in 1987 that 2 g/kg of ISG was synergistic with penicillin in decreasing bacteremia and mortality in neonatal rats injected with Group B *Streptococci* (112). Subsequently the same group reported an increased mortality when a large dose of IVIG was injected into rats (134, 442). Several large controlled studies of IVIG in neonates have failed to show an increased mortality in the treated neonates. Nonetheless, the risk of overwhelming the phagocytic system may be related to the dose infused, and it would therefore be prudent to use the lowest effective dose.

Aseptic meningitis – There have been several anecdotal reports of severe headache and vomiting occurring hours to days after infusions of IVIG (443–446). Most of the patients were adults treated for ITP, but several children have been reported and several others are known who have not been published. In each case the CSF white count was elevated to several hundred per mm³ and the protein moderately elevated to 0.10 to 0.50 g/L. In all cases the meningitis resolved spontaneously. Theories of

the mechanism of action include the development of immune complex disease, perhaps due to subclinical infection in the CSF, but little data are available. Anecdotally, pretreatment with corticosteroids (eg. 10 mg/kg of IV hydrocortisone) appears to prevent subsequent reactions, but no controlled studies have been conducted.

Hemolytic anemia – Preparations of IVIG usually contain low titers of anti-A, anti-B and anti-Rh(D), but these antibodies rarely cause symptoms when infused into patients. Indeed, it has been proposed that these antibodies coat red blood cells, causing them to be phagocytosed, thereby blocking the reticuloendothelial system and protecting antibody-coated platelets from destruction (267). Despite the usually benign nature of these antibodies, several cases of hemolytic anemia have been reported following infusions of IVIG. Some have been mild, resulting in a fall in hemoglobin without overt signs of hemolysis (447), or moderate, with mildly elevated bilirubin, fall in haptoglobin and requirement for transfusion (448–450). Severe intravascular hemolysis with hypotension and hemoglobinuria was reported in two blood group B, Rh(D)-positive patients infused with IVIG post bone marrow transplantation (451). Severe hemolysis was also reported after therapy of ITP with intravenous anti-D (452). Although these cases are well documented, it is not clear why these patients experienced adverse effects yet other patients with the same blood type, given the same preparations of IVIG, tolerated them without evidence of hemolysis.

Neutropenia – Intravenous gammaglobulin has been used successfully to treat autoimmune neutropenia. Paradoxically, there have been reports of transient neutropenia following infusions of IVIG. One patient was a 36 year old woman with SLE who had a transient fall in the white count for 5 days following each of two infusions (453). O'Donnell et al. (454) reported a patient who had neutropenia following infusion with an IVIG preparation made by the Commonwealth Serum Laboratory but not with Sandoglobulin. They hypothesized that the former contained more aggregates of IgG that could activate complement which might lead to altered expression of CR3 on the surface of neutrophils which would then adhere to endothelium. Transient neutropenia was also observed in a neonate given 1 g/kg of Sandoglobulin to treat alloimmune thrombocytopenia (455). The platelet count normalized but the neutrophil count declined to 450/mm³ at 15 days of life, 8 days after the third dose of IVIG. Anti-neutrophil antibodies were detected in the serum of the infant but not the mother. The exact lot of IVIG was not known, but anti-neutrophil antibodies were de-

tected by granulocyte immunofluorescence in one lot of Sandoglobulin and in a lot of American Red Cross IVIG. The neutrophil count spontaneously recovered by two months of age.

Pregnancy loss – There are no published reports of pregnancy loss as a result of infusions of IVIG. However, anecdotally several women have aborted within hours to days of receiving an infusion of IVIG. In one case, the woman experienced an acute reaction to the infusion and the onset of uterine contractions could have been the result of mediators such as prostaglandins that were released during the reaction. Unfortunately, no data are available regarding these alleged adverse reactions. Infusions of IVIG have been given to pregnant women with hypogammaglobulinemia (456), and to women with recurrent pregnancy loss secondary to antiphospholipid antibodies and lupus anticoagulant (360, 362) without adverse reactions and with benefit to both the mother and the fetus. Thus, despite the possibility of rare adverse reactions, women with hypogammaglobulinemia are at risk of developing serious infections and must be treated with IVIG; indeed, it may be necessary to increase the dose to compensate for the loss to the fetus. Infusions of IVIG should not be withheld during pregnancy if the clinical indication is clear and the benefits justify the small risk.

Miscellaneous adverse events – Several other adverse reactions have been reported in association with infusions of IVIG, but too few cases have been described to prove that the events were caused by the gammaglobulin.

Woodruff et al. reported four thrombotic events, three fatal, in 16 elderly patients infused with IVIG to treat autoimmune thrombocytopenia (457). They attributed the thrombosis to increased platelet activity as indicated by enhancement of ATP release. All of the patients had evidence of atherosclerotic disease and a previous history of infarction or hypertension. Subsequently, Frame & Crawford reported no incidents of thrombosis in 34 elderly patients treated with IVIG (458), though 2 had deep vein thrombosis thought to be due to other causes.

Several cases of acute renal failure following infusions of IVIG have been reported. Tan et al. reported a patient with chronic inflammatory demyelinating polyneuropathy and a second patient with ITP who developed acute renal failure after an infusion of IVIG (459). Prior to therapy both had mild elevation of creatinine to 1.6 mg/dl. On biopsy both had marked swelling and vacuolization of the proximal tubular epithelial cytoplasm similar to that seen with infusions of mannitol. Another patient with mixed IgM/IgG cryoglobulinemia secondary to a lymphoma developed renal failure after an infusion

of IVIG to treat a pulmonary infection (460). Biopsy showed hyaline thrombi in numerous glomerular capillaries and glomerular necrosis consistent with acute cryoglobulinemic nephropathy.

A single case of erythema multiforme was reported in a 27-year-old woman who was treated with IVIG for ITP (461). No other medication or antecedent illness could be implicated. Finally, three cases of alopecia were reported in women treated for ITP by Chan-Lam (462). In each case the patient was also treated with prednisolone. Examination showed telogen hair loss and biopsy did not reveal IgG deposition in the hair follicle. In each, the problem resolved spontaneously within four months.

Prevention and treatment of adverse reactions

With the IVIG preparations currently available, adverse reactions are uncommon in patients with normal immunity. However, patients with complete IgA deficiency are at risk for anaphylactic reactions if they are infused with IVIG preparations containing IgA. Such reactions, while rare, are potentially fatal and can be avoided by using preparations low in IgA, such as Gammagard®. If reactions do occur, they should be treated promptly with epinephrine, diphenhydramine, and corticosteroids.

Patients with antibody deficiency often experience immune complex mediated “phlogistic” reactions that were described above. Reactions are more common during initiation of therapy and during infections. Most reactions can be controlled by slowing or temporarily interrupting the infusion. Therapy with acetaminophen is helpful to reduce fever, muscle ache, and headache. Antihistamines should be used to treat urticaria, or angioedema, and inhaled β -agonists for wheezing or chest tightness. Patients who routinely experience adverse reactions should be pretreated with acetaminophen. Pretreatment with antihistamines is commonly used, but should be done with caution in patients who have experienced severe reactions since the antihistamine could mask the early signs of anaphylaxis such as pruritis. Some patients will tolerate one preparation better than others, and using a different preparation is preferable to using corticosteroids. Since adverse reactions are most common when therapy is first started, presumably because of a high antigen load, increasing the dose or decreasing the frequency of therapy will raise the antibody concentration and prevent reaccumulation of antigen between infusions. For patients who have persistent reactions despite these measures, pretreatment with corticosteroids has been effective in reducing symptoms and enabling completion of therapy (463–465).

Table 3. Possible mechanisms of action of IVIG

Proposed mechanism	Clinical example
Replacement of antibody	A- or hypogammaglobulinemia
Inhibition of F γ receptors	ITP (immediate effect), neutropenia, hemolytic anemia
Inhibition of complement (C3b)	ITP, vasculitis
Regulation of idiotype/anti-idiotype antibodies	Hemophilia due to anti-Factor VIII Guillain-Barré syndrome polyneuropathy, multiple sclerosis
Modulation of lymphocyte and monocyte function	Kawasaki disease, remission in ITP, cytopenias, GVHD

Mechanism of action of intravenous gammaglobulin

IgG has many physiologic effects and it is obvious that infusions of large quantities of IgG affect a diversity of systems. In addition to providing antibodies to a host of micro-organisms, normal IgG contains regulatory antibodies that may be directed against cell receptors or the idiotypic regions of other antibodies. Very high concentrations of IgG can also inhibit Fc receptors and adsorb complement components, thereby preventing phagocytosis and complement-mediated damage. Thus, there is not a single mechanism of action, but the effect of IgG depends on the system studied and the concentration of IgG present (Table 3).

Replacement of missing or defective antibodies

The original and most obvious use of IVIG is to provide antibodies in patients who are incapable of making functional antibodies. The effectiveness of the IVIG depends both on the titer of the various antibodies and the functionality of the antibody molecules. All of the currently available preparations have intact, unmodified IgG molecules that fix complement and bind to Fc receptors. The IgG subclass distribution is very close to normal. The antibody concentration represents that of several thousand normal, healthy donors. Normal individuals do not have very high levels of antibody unless they have been boosted by immunization or infection. That is not of importance to a normal individual who is primed and can readily respond by making more antibody. However, when antibody is replaced using IVIG only low levels of any specific antibody are provided. These levels may be adequate for prophylaxis, but are readily consumed and are not capable of treating infection. Thus, treatment may require much higher doses of standard IVIG or the use of specific high-titered preparations. One concern that has been recently raised is that as all high risk groups, especially HIV and hepatitis C positive individuals, are excluded from the donor pool, the over-

all levels of antibody in the serum pool will decrease. It is not known what effect this will have, but some pharmaceutical companies are considering plasmapheresis immunized donors, though that is technically more difficult and expensive. It will be important to monitor antibody levels during the next several years to be sure that we are providing adequate amounts of specific antibodies to the common pathogens.

Inhibition of Fc receptors

Many studies support Fc γ receptor (FcR) blockade as the most likely mechanism to explain the rapid increase in platelet count that occurs after infusion of IVIG (244). Fehr et al. (466) showed prolongation of the clearance time of antibody-coated red blood cells from the circulation by IVIG. Uptake of chromium-labeled platelets by the spleen and liver was transiently blocked in patients infused with 2 g/kg of IVIG (467). These observations are supported by the effectiveness of anti-Rh(D) antibody (274) as was discussed in the section on the treatment of ITP.

These clinical observations are supported by *in vitro* studies, though it is not known which Fc receptor is inhibited. There are three types of Fc γ receptors on human leukocytes. There are two high affinity receptors for monomeric IgG: FcRI (CD64) is present on mononuclear phagocytes and cytokine-activated polys, and FcRII (CD32) which is present on mononuclear phagocytes, polys, eosinophils, and platelets. Another receptor, with low affinity for monomeric IgG, binds aggregated IgG and immune complexes (FcRIII, CD16). It has an electrophoretic mobility of 51 to 72 KD and is found on neutrophils, NK cells, and macrophages, but not monocytes. Monomeric IgG in the fluid phase reversibly inhibits monocyte function, but if the IgG is first bound to a solid surface the inhibition is not reversible unless the IgG is enzymatically degraded (468). Presumably, the inhibition by insolubilized IgG involves localization of Fc receptors and function can not be restored until they are released. Loss of function is energy-dependent, involving ingestion, shedding or denaturation of receptors. Recovery required protein synthesis, suggesting that new receptors were generated. Salmon et al. (469) showed that treatment of human monocytes with 10 mg/ml of IgG inhibited Fc receptor-mediated phagocytosis of IgG-coated red blood cells, but did not alter internalization of neuraminidase-treated erythrocytes that are bound via the B-glucan receptor. These studies were consistent with their previous observations that monocytes from IVIG-treated patients with ITP demonstrated both decreased binding and ingestion of IgG-sensitized erythrocytes (470).

The most compelling evidence for the importance of Fc receptor function is the effect of anti-Fc antibody in patients with ITP. Infusion of the monoclonal antibody 3G8, directed against the 51–72 KD low-affinity Fc γ receptor CD16, resulted in a marked rise in the platelet count of a patient with refractory ITP (270). The long-term benefits were limited by the development of antibody to the mouse immunoglobulin, but the importance of FcR blockade was clearly demonstrated. Templeton et al. demonstrated that IVIG, as well as anti-Rh(D), contain significant amounts of anti-FcR antibodies, so that the effect of IVIG may not be mediated by non-specific binding of IgG to Fc receptors, but rather by specific effects of anti-FcR antibody (471).

Inhibition of complement and immune complexes

High levels of IgG may dissolve immune complexes that fix complement or could provide a “sink” to adsorb complement and thus prevent complement-mediated damage. Two different preparations of IVIG inhibited the formation of human albumin-rabbit anti-human albumin complexes (472). Addition of IgG promoted aggregation of preformed complexes. Both the pH 4-treated and the β -propiolactone-treated IVIG preparations inhibited complex formation, though the kinetics were different. These *in vitro* studies are supported by clinical observations. Patients with systemic lupus erythematosus have elevated levels of immune complexes measured by either C1q-binding or anti-C3 binding assays. After treatment of patients with IVIG, the levels of complexes measured by both assays decrease significantly (349). The mechanism of action is unclear, since incubation of IVIG *in vitro* with heat-aggregated IgG or immune complexes does not have any effect. It is possible that the IVIG alters the immune complexes to affect their clearance by the RES, but that is entirely speculative.

The binding of opsonized particles is markedly influenced by the presence of C3 on the surface (473). The C3b fragment of C3 binds to the Fd portion of IgG. The C3b/IgG heterodimer complex has unique properties: it can interact with phagocytes through both the CR1 receptor that recognizes C3b, as well as the Fc γ receptor, and it is resistant to degradation by Factors H and I and thus is more stable than C3b alone. Particles coated with C3b/IgG are opsonized or lysed more rapidly than particles coated with IgG alone. If red blood cells are coated with IgG alone, phagocytosis can be inhibited by high concentrations of IgG such as found in normal plasma; however, if the particles are coated with the C3b/IgG heterodimer, phagocytosis can not be inhibited even at the highest concentrations of IgG. Infusions of IVIG do not activate complement or

alter levels of complement components, but very high concentrations of IgG could bind C3b in solution, thus preventing formation of C3b/IgG complexes on opsonized particles (473).

Infusions of IVIG could prevent complement-mediated damage by mechanisms other than preventing phagocytosis. Guinea pigs infused with anti-Forsman antibodies die within minutes unless they are complement deficient. The Forsman antigen is present on endothelial cells and the antibody, in the presence of complement, destroys the endothelium leading to pulmonary edema, hemorrhage, and death. Normally 100% of the animals die within minutes, but up to 40% of the animals treated with 1 g/kg of IVIG before the Forsman antibody survived (473, 474). The effect was dose dependent and *in vitro* it was shown that the IVIG reduced the amount of complement-binding on the cell surface to zero. Thus, Frank et al. concluded that IVIG may act to prevent phagocytosis and complement-mediated damage by intercepting the activated C3b, forming heterodimers in solution, and thus preventing their formation on the surface of cells such as platelets, red blood cells, or endothelial cells. The effect is dose-dependent and requires very high concentrations of IgG, which is consistent with clinical observations.

Regulation of the anti-idiotypic antibody network

Regulation of antibody formation is very complex. Although it was initially thought that self-reactive clones were eliminated early in ontogeny, it is now obvious that normal individuals contain many autoantibodies, albeit in low concentrations. Antibodies against thyroglobulin, FcR, DNA and nuclear antigens, Factor VIII, and cytoskeletal proteins such as actin and tubulin are present in normal plasma (475). The levels of these autoantibodies are regulated by a complex network of anti-idiotypic antibodies, or antibodies directed against the V region of the antibody molecule (475, 476). Autoimmune disease may occur if this network is disturbed so that the concentration of one autoantibody increases and becomes pathologic. Since normal serum contains regulatory antibodies, IVIG may provide a means to restore the normal regulatory network.

The role of anti-idiotypic antibodies has been best described in hemophilia due to antibodies to Factor VIII. Spontaneous recovery from this disease is associated with development of antibodies that inhibit the pathologic anti-Factor VIII antibody (305). Preparations containing F(ab')₂ fragments from the post-recovery sera were shown to interact with F(ab')₂ fragments of the anti-Factor VIII antibody, thus demonstrating that these were anti-idiotypic antibodies. Treatment of some patients with IVIG results in

normalization of the clotting factors (303). Patients who respond to therapy with IVIG have a rapid fall in their levels of anti-Factor VIII antibody, whereas treatment failures do not show a decline (304). Incubation of serum from patients with anti-Factor VIII antibody with IVIG inhibits the autoantibody, in a manner similar to that observed with post-recovery IgG. Thus, there is strong evidence that anti-idiotypic antibodies are absent during disease and appear during the recovery phase of anti-Factor VIII induced hemophilia, and that normal sera contain these regulatory anti-idiotypic antibodies.

Other observations support the importance of anti-idiotypic antibodies in the control of autoimmune disease. Patients with spontaneous recovery from Guillain-Barré syndrome have anti-idiotypic antibodies in their sera that recognize a cross-reactive idiotype on anti-neuroblastoma cell line antibodies (312). As in the case of anti-Factor VIII antibodies, the activity was contained in F(ab')₂ portion of the IgG molecule and was directed against the F(ab')₂ portion of the anti-neuronal antibody. It is not yet known if these antibodies are present in normal sera. Normal sera do contain anti-idiotypic antibodies to anti-DNA, but the role of these antibodies in regulation of autoimmunity in SLE has not yet been demonstrated (477). Other idiotype-anti-idiotypic interactions will undoubtedly be described though progress will be slow due to the complexity of the system.

Modulation of lymphocyte function

Antibody-lymphocyte interactions

Normal human serum contains a wide variety of antibodies capable of interacting with lymphocytes. The anti-idiotypic antibodies discussed in the previous section are normally thought to interact with the V region of antibody molecules. B cells carry Ig molecules on their surface and thus could be targets for anti-idiotypic antibodies. The T cell receptor is an immunoglobulin-like molecule that can interact with anti-idiotypic antibodies, and recently autoantibodies against the T-cell receptor β chain were described (478), but thus far the regulatory effects of these antibodies are only speculative. It has been known for many years that normal sera, particularly from parous women, contain agglutinating and cytotoxic antibodies that can interact with T lymphocytes (479), and other studies demonstrated that the sera of pregnant women are inhibitory to T lymphocytes (480). Recently an antibody to the CD5 molecule that is present on T cells and a subset of B cells was discovered in IVIG (481). The effect of anti-CD5 has not yet been elucidated, but other anti-T cell antibodies have been shown to have inhibitory effects. For example, a rabbit antibody directed

against an LFA-1 like molecule on the surface of T cells and NK cells inhibited proliferation and cytotoxic activity (98). Antibodies directed against Class II HLA antigens are present in placenta-eluted gammaglobulin which have been shown to be very inhibitory both *in vivo* and *in vitro* (369).

Regulation of T and B cell function does not require antibodies to be directed against cellular components. IVIG preparations contain soluble CD4, CD8, and HLA molecules that could interfere with T cell activation. Recently, Takei et al. described several antibodies in IVIG preparations that are directed against staphylococcal superantigens (482). These superantigens have a dual affinity for both the Class II MHC antigens and the relatively invariant sequence of the β chain of the T cell receptor. Superantigens are thus capable of stimulating large numbers of T cells independently of the antigen specificity of the T cell. Superantigen stimulation has been implicated in diseases such as Kawasaki syndrome in which massive T cell stimulation occurs. Antibodies to the superantigens could block such stimulation and thus indirectly inhibit T cell activation. Finally, yet another potential mechanism of action for IVIG was recently described by Honda et al. (483). They described a sialic acid like substance in IVIG that could bind to the surface of platelets and prevent recognition by monocytes and macrophages. The importance of this unique inhibitory substance must be confirmed by additional studies.

Effects of infusions of IVIG on lymphocyte subsets and activity

Several studies have reported that infusions of IVIG can alter the numbers and percentages of lymphocytes and NK cells in the peripheral blood, and that the activity of the remaining cells is altered. The first was the observations of Durandy et al. that injections of gammaglobulin into normal children impaired the ability of B cells to mature into plasma cells when stimulated *in vitro* with pokeweed mitogen (484). They attributed this to an increase in a suppressor T cell that lacked Fc γ receptors, and presented evidence that activation of the T suppressor cells was induced by excessive PGE₂ production by monocytes. Delfraissy et al. (485) measured suppressor activity in adult patients with ITP before and after treatment with IVIG. In the five of seven patients who responded to therapy, there was an increase in Con A induced suppressor activity for autologous *in vitro* B cell immunoglobulin production. The two patients who failed to respond had no alteration in suppressor activity. In their study, there was no alteration in lymphocyte subpopulations in any patient. Similar results were obtained by Tsubakio et al.

in five adult patients with ITP (486). The proportion of CD3 cells did not change, but the CD4: CD8 ratio decreased significantly and there was a 78%, 48%, and 66% suppression in *in vitro* synthesis of IgG, IgA, and IgM, respectively. They also noted a decrease in the titers of various autoantibodies in addition to the antiplatelet antibodies involved in the ITP.

In marked contrast to these studies, extensive evaluation of eight ITP patients by Bussel et al. (487) led to the opposite conclusion. All of their patients had reduced *in vitro* immunoglobulin production prior to therapy with IVIG, and most normalized after treatment. They observed a decrease, not an increase, in suppressor activity measured by co-culture of mononuclear cells from the patient with cells from a normal donor. There also was a decrease in the amount of platelet bound IgG, but overall immunoglobulin production was increased after IVIG therapy. The reason for the discrepancy is not clear. In the study by Bussel, production of Ig plaque-forming cells was measured rather than production of immunoglobulin, but that should not lead to such disparate results. Bussel noted that all of their patients were treated with corticosteroids at the onset of therapy and most were able to discontinue steroids after IVIG. Corticosteroids are capable of suppressing Ig synthesis, but also decrease suppressor activity, so the role of the steroids, if any, is unclear. Further study of previously untreated patients might clarify the reason for these differences.

Alterations in immune function after IVIG therapy have been observed in a variety of other illnesses. When adult patients with CVID were infused with IVIG for several months, they had a decrease in the absolute number of CD3 and CD4 T cells, with a relative increase in CD8 cells and suppressor activity measured against normal B cells (488). All of the patients had intrinsic B cell disorders and that did not change with IVIG therapy.

The absolute number of T cells and polys decreased in the majority of patients with myasthenia gravis after treatment with IVIG (333). An increase was observed in the number of immunoglobulin-bearing cells, but it was not due to an increase in B cells since the percentage of CD19+ cells did not increase. The most significant change was an increase in the percentage of CD16+ NK cells from 11% pretreatment to 24% in the 24-h post infusion samples, but the change was probably due to a decrease in the T cells rather than an increase in NK cells. The percentage of NK cells normalized by one week post therapy. The percentage of cells expressing Leu 7 (CD57), a marker of a subset of NK cells, did not change. They did note a change in the CD4:CD8 ratio, but this was due primarily to an increase in a population of weakly positive CD8 cells which may have been NK cells.

Markedly different results were obtained in a study of patients with multiple sclerosis; the absolute numbers of T cells, B cells, and NK cells were significantly suppressed for up to five weeks after infusion of 1.6 g/kg of IVIG (489). All of the lymphocyte subsets appeared to have been equally affected so that the ratios did not change. NK cells recovered most rapidly and were nearly normal at three weeks, whereas B and T cells required five weeks to return to normal. No evaluation of function was done in this study.

Several studies have looked at the effects of infusions of IVIG on NK cell number and activity. Natural killer cell activity was markedly reduced following IVIG infusions in patients with agammaglobulinemia or ITP (490). It was not possible to determine if this was due to a decrease in the number of NK cells, but they did note that the addition of IVIG to the NK assay markedly inhibited killing of K562 target cells. Of interest, they also noted a decrease in NK activity when sucrose or maltose, the sugars present in Sandoglobulin and Gamimune, were added to the NK assay, though the inhibition was far less than that observed with IVIG. In contrast, no alteration in NK activity was observed in preterm infants infused with 500 mg/kg of IVIG, a dose that increased their IgG concentration to that seen in term infants (491). They did not study the effects of higher doses and evaluated the patients immediately after the infusion. Finberg et al. (492) found a transient decrease in NK activity immediately after an infusion of IVIG in patients with Kawasaki disease, but that was followed by a marked increase in the relative and absolute numbers of CD16+ NK cells and NK activity. They also observed an increase in antibody-dependent cell-mediated cytotoxicity (ADCC) which is also thought to be mediated by CD16+ cells.

It is difficult to compare the results of all of these studies because of differences in the patient populations and the methods used to evaluate immune function. The majority of studies suggest that suppressor activity is increased following therapy with IVIG and that autoantibody formation and, in some cases, non-specific immunoglobulin production, are decreased. However, conflicting results have been reported. In some reports suppressor cells increase following IVIG therapy, but in others total T cells and NK cells are reduced. Interpretation is difficult since patients may not have normal subsets or *in vitro* immunoglobulin production prior to therapy because of their disease or therapy with drugs such as the corticosteroids. The response of patients with one disease may not be representative of all patients or normal individuals. Clearly, a great deal of additional study is required before we can understand the effects of infusions of IVIG on the immune system.

Regulation of lymphocyte function

In vitro studies allow evaluation of the effects of IVIG on immune cells under relatively controlled circumstances and have yielded valuable data on the effects of IgG on immune cells. Unfortunately, *in vitro* studies are prone to artifact and conflicting results have been reported. One of the first observations was that of Durandy et al. (484) discussed in the previous section. They treated immunologically normal children who had recurrent infections with intramuscular injections of IgG and noted that their B cells failed to produce plasma cells when stimulated with pokeweed mitogen *in vitro*. They found that when the IgG preparations were added to cultures of normal cells, lymphocytes were unable to proliferate and maturation of B cells was abolished. The inhibition was due to development of suppressor activity that was dependent on the presence of monocytes and mediated through PGE₂. Once T cell suppressor activity developed, the monocytes were no longer necessary.

Several subsequent studies have confirmed the inhibitory effects of IgG on B cell maturation and immunoglobulin synthesis. Stohl (493, 494) reported that Sandoglobulin in concentrations of 300 µg/ml inhibited the development of pokeweed mitogen-induced plaque-forming cells. He found that the IgG had to be present at the initiation of the culture to exert its suppressive effect and that F(ab')₂ fragments were not effective. Removal of the IgG after 24 h in culture did not permit the B cells to mature normally. In this system the IgG appeared to affect the B cells directly, and no augmentation of T cell suppressor activity or inhibition of T cell help could be demonstrated.

Hashimoto et al. (495) also demonstrated inhibition of B cell maturation, though they reached different conclusions regarding the mechanism of action. They evaluated ISG and several different IVIG preparations and found that the ISG was most inhibitory, followed by the sulfonated and PEG preparations, but that a pepsin-treated IVIG preparation was not inhibitory. Thus, their results confirmed those of Stohl (493) that an intact Fc portion of the IgG molecule was necessary for it to inhibit B cell maturation. They incubated the IgG preparations with subsets of mononuclear cells and found that pretreatment of either the B cells or T cells resulted in inhibition, but that T cells depleted of CD8⁺ cells were not effective. Unlike Durandy et al. (484), Hashimoto et al. were not able to demonstrate a role for monocytes or PGE₂ in the development of suppression.

Buckley et al. (480) reported the inhibitory effects of pregnancy sera and IgG fractions obtained from those sera on lymphocyte proliferation induced by

mitogens, antigens, and allogeneic cells. Subsequent studies indicated that IgG from normal donors had similar properties (496, 497). Concentrations of IVIG from 1 to 10 mg/ml inhibited lymphocyte proliferation in a dose dependent manner. Proliferation induced by allogeneic cells and anti-CD3 monoclonal antibody was particularly sensitive. Inhibition was reversible if the IgG was washed out of the cultures within 48 h, indicating that it was not due to a cytotoxic effect. Kawada & Terasaki published the first detailed reports of the inhibitory effects of IgG (498). They demonstrated that IgG concentrations of 20 to 30 mg/ml inhibited PHA stimulation, mixed lymphocyte culture, NK cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and cell-mediated lympholysis. They also showed that Fc fragments were more effective than intact IgG molecules.

The mechanism of suppression was investigated in an animal model by Shimozato et al. (499). They found that concentrations of pH 4 IVIG as low as 0.5 mg/ml inhibited tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) by rabbit peritoneal exudate cells stimulated by lipopolysaccharide. Interaction of the PEC with the IgG stimulated cAMP. Blocking cAMP production prevented IgG-mediated suppression and stimulators of cAMP inhibited synthesis of TNF-α and IL-1. Thus, interaction of the IgG with the Fcγ receptor on macrophages induced cAMP which inhibited cytokine production. Anderson & Andersson demonstrated that monokine production by human monocytes is similarly suppressed by IVIG (500). Production of IL-6 by monocytes stimulated with lipopolysaccharide was inhibited by concentrations of IVIG from 0.6 to 12 mg/ml in a dose-dependent manner, but, unlike the rabbit peritoneal macrophages, monocyte production of TNF-α was not inhibited.

A recent study by van Schaik et al. confirmed the inhibitory effects of IVIG on *in vitro* proliferation and examined the kinetics of the inhibition (501). Concentrations of IVIG from 1 to 50 mg/ml inhibited the response to allogeneic cells up to 80%. IL-2 stimulated cells were maximally inhibited by 15 mg/ml, and PHA stimulation by 35 mg/ml. Preincubation of stimulator and responder cells and washing prior to culture did not result in inhibition. When IgG was added at the beginning of mixed lymphocyte cultures and washed out at various times after initiation of culture, no inhibition was observed if the IgG was removed after 2 to 4 h, but proliferation was inhibited if the IgG were present for 12 to 24 h. If addition of IgG was delayed until the cultures were established, inhibition of allogeneic cell or PHA-induced proliferation was observed even if addition of IgG was delayed until 4 h before addition of ³H-thymidine. Interestingly, IgG had an inhibitory

effect on a wide variety of spontaneously growing cell lines, independent of the species of origin or the source of the cells. The IgG was not cytotoxic for the cells that were found to be arrested in the G₀/G₁ phase and not able to progress to the S phase. Taken together, these experiments suggest that IgG inhibits late in the proliferative phase rather than during initial stimulation.

These experiments indicate that IgG is able to modulate a wide variety of immunologic functions. It is likely that it acts through multiple mechanisms. Inhibition of phagocytes and NK cells may occur through interaction of the Fc portion with the FcγR such as FcRIII, whereas the irreversible inhibition of B cells by very low concentrations of IgG might involve binding of aggregates or anti-idiotypic antibodies. Inhibition of T cells requires very high concentrations of IgG and appears to occur late in the proliferative cycle. Whether this involves blocking of cytokines or anti-idiotypic like antibodies that can interact with the T cell receptor or other regulatory molecules on the surface of the T lymphocyte is unknown and will be the subject of future experiments.

Summary

Approved uses of IVIG

Other than FDA approval for primary immune deficiency, ITP, and CML, there is no official designation of "approved" for any use of IVIG, though its use in some situations is better defined than in others (Table 2). Even the NIH Task Force report (502) equivocated in many situations. In some conditions the benefits of therapy are so well demonstrated that withholding treatment would be not be considered good medical practice; this is probably true only for treatment of patients with antibody deficiency and Kawasaki Disease. There is no question that IVIG is highly effective for the treatment of ITP, particularly in children, but in some patients the thrombocytopenia resolves spontaneously and others resolve with a short course of corticosteroids. Thus, not every patient must be treated with IVIG, though its use is reasonable and justified in the appropriate clinical setting.

The use of IVIG is supported by controlled trials in a number of other diseases, but in none are the data incontrovertible. Several controlled studies support the use of IVIG for transplant recipients, neonates, Guillain-Barré Syndrome, myasthenia gravis, multiple sclerosis, chronic demyelinating polyneuropathy and CML. In each situation there are conflicting studies, but it is likely that at least a subset of patients would benefit. Further studies are needed to define the dose and schedule, and whether specific high-titered preparations are required, and

to select the patients who are most likely to respond. In special circumstances, such as transplant patients who are at very high risk of infection and GVHD, or patients with polyneuropathy who are refractory to all other forms of therapy, the use of IVIG is probably justified until further studies can be completed.

There remain a host of diseases in which there are anecdotal reports of efficacy for which the use of IVIG is intriguing but as yet there is insufficient evidence to justify its routine use. These include the collagen-vascular diseases, inflammatory bowel disease, asthma, diabetes, hemophilia due to Factor VIII autoantibodies, secondary immunodeficiencies such as trauma and burns, and specific infections including Group B *streptococcus*, *Pseudomonas*, RSV, and parainfluenza. In the future either IVIG or special immunoglobulin preparations may prove to be of benefit in these diseases, but a great deal of additional research is required and the use of IVIG in these situations should be confined to the research setting.

Cost benefits

Cost-benefit analysis is certainly an important consideration today and undoubtedly will become more important in the future. However, it is important to recognize that not all costs are financial or can be measured in terms of time lost from work or school. Even if it were less expensive to treat infections in a patient with agammaglobulinemia than it is to treat prophylactically with IVIG, it would be impossible to withhold therapy that could be potentially life-saving. Similarly, it would be medically unacceptable to choose to treat coronary artery disease in a child with Kawasaki Disease rather than to try to prevent aneurysms with IVIG. Even in a situation where the use of IVIG is not always required, such as ITP, it is difficult to justify splenectomy if IVIG able to obviate the need for surgery. Obviously, the cost must be considered, but not at the expense of good medical practice.

In situations where the use of IVIG is more controversial, or where there are other equivalent alternatives, then cost considerations become more important. Future studies must include evaluation of costs, such as decreased length of hospitalization, use of antibiotics, and need for surgery, as well as the quality of life and lost income. Determination of efficacy and cost-effectiveness will require large, multicenter, collaborative studies that should involve physicians, pharmaceutical companies, and the insurance industry (503).

Areas of future investigation

There is a need for research in every aspect of the use of IVIG. In the future questions of efficacy must be addressed in double-blind, placebo-controlled studies involving large multicenter collaborative groups. Issues of cost and safety must be considered in an objective manner.

It is vital that we have a better understanding of the mechanisms of action of IVIG in each situation in which it is used. Improved understanding of idiotype regulation and interactions of IgG with cells of the immune system, both through Fcγ receptors and by Fab interactions with specific cellular antigens, should lead to development of preparations that contain specific regulatory antibodies. It is likely that these antibodies could be generated using molecular biology techniques and used alone or to "spike" IVIG preparations. Similarly, hyperimmune preparations to a variety of microbial pathogens will be needed in the next generation of studies evaluating the role of IVIG in specific infections. Although some of these sera could be prepared from immunized donors or by selecting donors having high titers of antibody to the organism of interest, it is likely that it will be necessary to generate a large assortment of humanized monoclonal antibodies to be used in combination against each organism.

The use of IVIG has been life-saving to patients with primary disorders of antibody production and has provided many patients with a safe alternative to immunosuppressive drugs. The results in collagen vascular disease, cytopenias, chronic inflammatory demyelinating polyneuropathies and Guillain-Barré Syndrome are encouraging and have given us exciting insights into immune regulation. Further studies are desperately needed to enable selection of those patients most likely to respond, to determine the proper dose and schedule, and to develop IVIG preparations enriched in the specific antibodies needed to control each disease.

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