

Special Article

Intravenous Immunoglobulin (IVIG) for the Therapy of Autoimmune Disorders

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The weight of evidence from numerous clinical studies supports the use of IVIG, particularly at higher doses, in the treatment of a wide range of autoimmune disorders. Extensive experience has documented the safety of IVIG therapy but its present relatively high cost necessitates firmly establishing its efficacy. There is an acute need to define those disease states where IVIG is indicated and effective. Large-scale, possibly multicentered, clinical trials employing rigorous controls will resolve these questions. Concurrent fundamental immunologic studies will elucidate the mechanisms underlying the clinical effects. We are experiencing an exciting new era of effective immunotherapies and intravenous gamma-globulin preparations have already secured an important place in the therapeutic armamentarium. While one must guard against unsubstantiated applications, critical exploration of new uses for this unique product is warranted.

KEY WORDS: Intravenous immunoglobulin; autoimmunity; immunomodulation.

INTRODUCTION

Antiinflammatory and immunosuppressive drugs have been the primary agents for the treatment of autoimmune disorders. While our understanding of the scope and pathogenic mechanisms of autoimmune diseases has expanded greatly, newer forms of therapy have also been proposed and developed. Included among these are plasmapheresis, antiidio-

typic antibodies, and biological response modifier substances.

Gamma-globulin replacement is the definitive treatment for humoral immunodeficiency disorders. With the advent of intravenous immunoglobulin (IVIG) preparations, therapeutic application was extended to, among other indications, the treatment of idiopathic thrombocytopenia purpura (ITP). Because of the role of antiplatelet antibodies in the pathogenesis of ITP, it can be considered to have an underlying autoimmune etiology. The mechanism(s) of action of IVIG in the treatment of ITP remains poorly understood. However, two hypotheses have gained popularity: (i) Fc receptor blockade and (ii) antiidiotypic antibodies directed against the autoantibodies. Based upon earlier use of IVIG in the treatment of ITP associated with antiplatelet autoantibodies, this therapy has been extended to the wide variety of other autoimmune disorders. Gupta (1) has previously described many of these applications; the present review updates and extends his earlier report. As used herein the definition of autoimmune disease is very broad and encompasses a host of conditions where the underlying immunopathogenic mechanisms include the presence of autoantibodies.

SPECIFIC DISEASES

Idiopathic Thrombocytopenia Purpura

Although the original and primary indication for IVIG replacement therapy remains antibody defi-

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ciency states, its use in the treatment of both acute and chronic ITP has also been approved. Imbach and colleagues (2) were the first to report on the efficacy of treatment of ITP of childhood with high-dose IVIG. The initial rationale for this form of therapy was the observation that two congenitally agammaglobulinemic patients with severe thrombocytopenia manifested significant increases in platelet counts after administration of IVIG. IVIG was also found to be effective in treating thrombocytopenia associated with the Wiskott-Aldrich syndrome (3), a disorder in which the presence of platelet-associated antibodies has been described (4). From these earlier studies numerous others have emerged (see Ref. 5 for a review). As the subject of IVIG for the treatment of ITP has been extensively reviewed previously, only a limited discussion is presented here. Lusher and Warrier (6) specifically distinguished between the use of IVIG to treat acute, postinfectious ITP of childhood and its use to treat chronic, autoimmune ITP, which generally affects adults. While the former is often a benign, self-limited disease with a high probability of spontaneous remission, the latter tends to be resistant to corticosteroids and may thus be more amenable to IVIG therapy, possibly in preparation of splenectomy.

Management of acquired, immune thrombocytopenias with IVIG has also been described by several investigators. It has been shown that thrombocytopenia due to alloimmunization after platelet transfusions can be ameliorated by high-dose IVIG therapy (7-11), as can posttransfusion purpura (12, 13), neonatal immune thrombocytopenia (14-16), and autoimmune thrombocytopenia of pregnancy (17, 18). Although the latter syndromes are not classical autoimmune disorders as they reflect *de novo* sensitization, nevertheless, their underlying pathogenic mechanisms are very similar to autoimmune phenomena.

Hemophilia Associated with Antihemophilic Factor Inhibitors

While classic hemophilia is an X-linked disorder of blood coagulation due to a nonfunctional variant of antihemophilic factor (factor VIII), acquired inhibitors of antihemophilic factor have been described which cause a coagulopathy clinically similar to hemophilia. These inhibitors have been identified as antibodies. A 39-year-old patient with hemophilia B was found to have circulating antibod-

ies capable of functionally inhibiting factor IX (19). These antibodies were probably of the IgG class, as they could be removed by protein A-Sepharose chromatography. However, when extracorporeal treatment by protein A-Sepharose adsorption was attempted, the patient subsequently developed a 15 fold increase in antibody titer. When immunoadsorption was followed by IVIG, no such rebound phenomenon was observed, and it was followed up by a prolonged suppression of anti-factor IX antibody production.

Replacement therapy with purified factor VIII for the treatment of hemophilia is sometimes complicated by the development of inhibitory antibodies against factor VIII. Two such patients treated with high-dose IVIG, however, showed a significant rise in inhibitor titers after treatment (20). In contrast, two other reports described the successful treatment of patients with hemophilia A and serum factor VIII inhibitors (21, 22). Clinical improvement was paralleled by the disappearance of inhibitory anti-factor VIII antibodies and resulted in prolonged remission lasting at least 7 months. Follow-up was unavailable. At present it is not possible to predict which patients with hemophilia and antihemophilic factor antibodies will respond to IVIG. Although empirical therapy can resolve the question, it must be pointed out that such treatment has been complicated by a significant rise in inhibitor titers, thus making factor VIII replacement even more difficult.

Sultan and colleagues demonstrated that treatment of hemophilia due to autoantibodies against antihemophilic factor (factor VIIIc) with IVIG was associated with the presence of antiidiotypic antibodies against the pathologic autoantibodies within the immunoglobulin preparation (23). This was based on the observation that the *in vivo* clinical response was correlated with the ability of an F(ab')₂ fraction of the immunoglobulin preparation to reverse the inhibition of factor VIII activity by autoantibodies from hemophilic patients *in vitro*.

Autoimmune Hemolytic Anemia

Immunosuppressive drugs with or without plasmapheresis or splenectomy have been the principal treatment modalities for severe autoimmune hemolytic anemias. Earlier reports suggested that IVIG therapy was ineffective in treating autoimmune hemolytic anemia particularly of the "warm" (IgG-

mediated) type (24, 25). However, IVIG has been used to successfully treat a case of Evans syndrome, refractory autoimmune hemolytic anemia with ITP (26). The rationale for the use of IVIG in this setting was its previously demonstrated efficacy in ITP and presumed similar immunopathogenesis of hemolysis and thrombocytopenia. In this case of a 5-month-old boy, who failed to respond to high-dose pulse therapy with corticosteroids and subsequent cyclophosphamide administration, remission was achieved rapidly after two courses of 1.6 g of IVIG/kg given over 4 days. Although the patient was also on chronic prednisone, it was gradually withdrawn and discontinued after IVIG treatment without relapse. Similarly a 75-year-old man with idiopathic warm autoimmune hemolytic anemia who had been unsuccessfully treated with prednisone, azathioprine, and splenectomy showed immediate but transient improvement after two courses of high-dose IVIG (27). A third course of treatment resulted in a prolonged remission. IVIG has been deemed particularly useful when autoimmune hemolytic anemia is associated with immunodeficiency syndromes (28). Several other reports substantiate the use of IVIG in autoimmune hemolytic anemias due to hemolytic antibodies of the IgG class (29–31).

Although pure red-cell aplasias are distinctly different from hemolytic anemias in that erythroid precursor cells of the bone marrow are usually absent in the former, many cases of pure red-cell aplasia may be due to immune suppression of erythropoiesis by IgG autoantibodies. McGuire *et al.* described the successful treatment of a 4-year-old girl with antibody-mediated, pure red-cell aplasia (32). Since both F(ab')₂ fragments and intact IgG molecules from pooled donor gamma-globulin could reverse the cytotoxic activity of the patient's IgG fraction on hematopoietic progenitor cells *in vitro*, they concluded that the therapeutic effect may be due to antiidiotypic antibodies recognizing the patient's IgG autoantibodies.

One patient, a 60-year-old man, with a presumed autoimmune pure white-cell aplasia has also been treated with high-dose IVIG (33). Although a rapid remission was achieved, it was short-lived, requiring other therapeutic intervention.

Autoimmune Neutropenia

Only a few studies have demonstrated the efficacy of IVIG in the treatment of autoimmune

neutropenia. An early report by Pollock *et al.* (34) showed a transient response of autoimmune neutropenia to high-dose IVIG. It was subsequently demonstrated that IVIG produced a more protracted improvement in two symptomatic children with autoimmune neutropenia of infancy (35). The increased neutrophil count was associated with normal functions and evidence was presented suggesting that IVIG may work through Fc receptor blockade and/or decreased antineutrophil antibody synthesis. Similar positive effects of IVIG on autoimmune neutropenia were also observed in other studies (36–38).

Felty's syndrome is an autoimmune disease consisting of neutropenia, splenomegaly, and rheumatoid arthritis. The neutropenia appears to be secondary to production of antineutrophil antibodies. Several patients with Felty's syndrome have been treated with IVIG but failed to respond to therapy (39, 40). As this observation conflicts with reports of the successful treatment of other immune cytopenias with IVIG, it has been suggested that the neutropenia of Felty's syndrome may involve different pathologic mechanisms (40).

Murakami *et al.* (41) reported an interesting dissociation between the response of autoimmune neutropenia and thrombocytopenia in a 15-year-old girl. The neutropenia initially responded to IVIG but the thrombocytopenia did not. On subsequent treatment both neutrophil and platelet counts increased significantly. Again, it was suggested that different immunopathogenic mechanisms may be involved in various autoimmune cytopenias.

In another case of combined autoimmune thrombocytopenia and neutropenia, Ricevuti *et al.* examined the effect of exogenous IVIG on a variety of neutrophil functions (42). Most significantly was the coincident improvement of depressed neutrophil chemotaxis after treatment. This was paralleled by a disappearance in antineutrophil autoantibodies over a 6-day period. Within 30 days, antineutrophil antibodies reappeared and neutrophil numbers and chemotaxis were again depressed. It was also interesting to note that the serum of the untreated patient could suppress the mobility of normal donor neutrophils, but after IVIG treatment the patient's serum was no longer inhibitory. After 30 days, the patient's serum was again suppressive of chemotaxis coincident with the return of neutropenia and antineutrophil antibodies.

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder wherein autoantibodies to the acetylcholine receptor at the myoneural junction block normal transmission of impulses from the nerve terminus to the muscle fiber. Clinical manifestations of MG include motor weakness and easy fatigability. Therapy of MG includes the use of anticholinesterases to potentiate and prolong the signal at the motor end plate as well as immunosuppressive therapy including corticosteroids and azathioprine. Early preliminary reports suggested that high-dose IVIG could result in neurologic improvement and diminution of acetylcholine receptor antibodies (43, 44). While improvement has been further reported in MG (44, 46), no change in acetylcholine receptor antibodies was noted in another study (47). In a more extensive series and report, Arsura *et al.* described similar beneficial effects of high-dose IVIG to treat and produce sustained improvement in 11 patients with MG (48). It was interesting to note that the response to IVIG therapy was independent of a variety of parameters including previous therapy, coexisting thymoma, or a history of thymectomy. In contrast to some previous reports, no depression of elevated acetylcholine receptor antibody titers was observed despite clinical improvement.

Cook and her colleagues have described some interesting changes in immunologic parameters occurring during the course of IVIG treatment of MG (49). While a slight decrease in the total number of circulating lymphocytes was observed, CD16⁺ and CD8⁺ mononuclear leukocytes showed a significant increase proportionate to the serum level of IgG achieved. The authors speculated that these might represent natural killer cells. Other findings included an increase in IgG-specific, Fc receptor-bearing cells which could potentially be suppressor T lymphocytes and decreases in the absolute number of helper T cells. The latter observations may partially elucidate the immunoregulatory mechanisms underlying the efficacy of high-dose IVIG for the treatment of MG.

Seizure Disorders

The inclusion of seizure disorders within the category of autoimmune diseases is admittedly arbitrary. However, evidence does exist for the role of immunologic mechanisms in the pathogenesis of some forms of epilepsy (50). Several investigators

have utilized IVIG for the treatment of intractable childhood epilepsies, with a wide range of results (51–56). Although perceived clinical improvement could occasionally be correlated with objective neurologic evidence, all of these reports lacked rigorous controls.

Regarding hypothetical mechanisms of action of IVIG in the treatment of seizures, it is interesting to note that for some of the specific seizure types described, immunosuppressive drugs (e.g., adrenocorticotropic hormone and/or corticosteroids) have been used in conjunction with anticonvulsants. Thus one could speculate that IVIG may be operating through a putative immunomodulatory mechanism. In seizures associated with a specific immunodeficiency (57, 58), IVIG may be exerting an effect against an etiologic agent. Again, these questions will only be resolved with large-scale, well-controlled, prospective clinical trials.

Multiple Sclerosis (MS)

MS is a demyelinating disease of unknown etiology; however, considerable evidence exists for the role of immune mechanisms in its pathogenesis. A popular model includes a proposed initial viral infection followed by a secondary autoimmune process, principally directed at the perineural myelin sheaths. In extreme reactions the axis cylinders are also affected. Therapy has generally consisted of immunosuppressive drugs, principally ACTH and corticosteroids, plus symptomatic treatment. However, several investigators, primarily in Europe, have also employed IVIG. These trials, like numerous others described herein, have been unblinded and nonrandomized with minimal controls. In an early attempt at using IgG to treat MS, Schuller and Govaerts (59) initially used intramuscular gammaglobulin, 5 g, given three times per week. This was subsequently changed to IVIG, 5 g, given once weekly. Their cohorts consisted of 31 MS patients with a mean duration of therapy of 4 years. The clinical course of these patients was compared to that of a control group of 164 patients receiving conventional therapy. Three response profiles were observed: (i) improvement (11 patients), (ii) no changes (9 patients), and (iii) deterioration (11 patients). When compared to the course of the controls, the degree of improvement noted in the first group was statistically significant by several tests.

In another trial Rothfelder *et al.* (60) treated 20 MS patients with 5 g of IVIG administered every 2

months. Some clinical improvement, primarily in extremity symptoms, was noted, as well as a decrease in the frequency of exacerbations. These authors concluded that more extensive and better-controlled additional trials are warranted.

A summary of the experience of using gamma-globulin to treat MS has recently been published (61). While it was recognized that it is still too early to judge the efficacy of gamma-globulin in the treatment of MS, it was also noted that some patients with severe, progressive exacerbations seemed to experience rapid neurological improvement with gamma-globulin treatment.

Inflammatory Polyneuropathy

Chronic polyneuropathies can occur in conjunction with other disorders such as infections, malignancies, and collagen-vascular diseases or they may be idiopathic in origin. While their underlying pathologic mechanisms may be obscure, the frequent occurrence of mononuclear infiltrates of the affected nerves suggests the possibility of associated immunopathology. Accordingly Vermeulen and colleagues have treated 17 patients with chronic inflammatory polyneuropathy with fresh-frozen plasma or high-dose IVIG (62). Improvement was observed in 13 of these patients. The rationale for this therapy was based on the effects of IVIG for ITP. Of particular significance was the observation that improvement was seen after plasma or IVIG, in spite of the fact that no spontaneous remissions had been noted for 2 months prior. When plasma or IVIG was discontinued, the patients deteriorated clinically; however, upon reinstating treatment they experienced significant improvement. Although the treatment effect was short-lived, improvement could be reestablished with plasma or IVIG infusions, without any indication of becoming refractory to chronic therapy. The authors further suggest trials of IVIG for acute polyneuropathies.

Systemic Lupus Erythematosus (SLE)

Only a limited experience with IVIG treatment of SLE has been reported to date. Gaedicke *et al.* described the widely disparate responses of two adolescent girls with SLE to treatment with high-dose IVIG (63). While one patient achieved a long-lasting remission of a serious, acute exacerbation, no effect was seen with the other patient. It was implied that IVIG may be effective for ameliorating

severe acute exacerbations of SLE but may not be of use in chronic disease, which may explain the different responses observed.

Additional reports have also indicated marginal effects of IVIG on SLE. When six patients with SLE were treated with high-dose IVIG, the only clinical response was a brief improvement in their thrombocytopenia (64). Other symptoms generally remained unchanged; however, proteinuria increased secondary to IgG appearing in the urine. Circulating immune complexes, which were elevated prior to therapy, showed significant posttreatment reductions. Two infants born to mothers with active SLE who showed significantly decreased platelets and polymorphonuclear neutrophils soon after birth were treated with IVIG (65). Rapid amelioration of the children's cytopenias was observed. Recently two independent groups described the use of IVIG for several different patients with various collagen vascular disorders including SLE, juvenile rheumatoid arthritis, polymyositis, and Sjogren's syndrome (66, 67). While improvement and steroid sparing activity was noted, some of the effects were transient. These observations suggest that criteria for patient selection and optimal dosage remain to be determined.

Although several unpublished reports on the use of IVIG in the treatment of SLE, including lupus glomerulonephritis, have also been presented at various meetings, it is still premature to determine the role of this therapy for SLE. More extensive, well-controlled trials may soon resolve this issue.

Rheumatoid Arthritis

Like SLE, a paucity of published studies begs the question of whether IVIG may be useful in the treatment of rheumatoid arthritis (RA). In a very early report, Sany and co-workers describe the treatment of 10 hospitalized patients with severe RA using intravenous administration of a gamma-globulin preparation derived from human placentas (68). Significant but transient clinical improvement was noted in seven patients. A concomitant increase in both lymphocyte mitogen responses and percentages of "active" (E-rosette) T cells was also observed. In a much larger series of 31 patients with RA, approximately 60% of the study population experienced significant clinical improvement after the intravenous administration of a similar placenta-derived gamma-globulin preparation (69). While variable improvements were noted with regard to

the sedimentation rate and levels of rheumatoid factor, ANA, and levels of circulating immune complexes, all patients showed increased active E rosette-forming cells and a short-lived decline in Fc receptor-bearing lymphocytes. It was implied that in both of these studies the placental source of the gamma-globulins may have endowed them with unique immunosuppressive properties (e.g., anti-HLA-DR activity).

Kawasaki Syndrome

Kawasaki disease (KD) or mucocutaneous lymph node syndrome consists of a constellation of signs and symptoms including (i) fever of unknown etiology lasting 5 days or more, (ii) bilateral injection of the ocular conjunctivae, (iii) perioral and oropharyngeal changes and inflammation, (iv) cervical adenitis, (v) involvement of extremities (palmar and plantar erythema, edema, and desquamation), and (vi) polymorphous truncal examthem (70). Although the basic pathogenic mechanisms underlying KD are presently poorly understood, nevertheless, much evidence indicates that it may be an immunologically mediated disorder. Because of a presumed immunologic basis for KD, especially the presence of potentially pathologic soluble circulating immune complexes, Furosho *et al.* undertook a multicenter, controlled trial of high-dose IVIG plus aspirin versus aspirin alone for the treatment of patients with KD (71). They reported that the IVIG regimen appeared to reduce the frequency of coronary artery abnormalities. These results were confirmed in a subsequent controlled, American study (72). Hence the Committee on Infectious Diseases of the American Academy of Pediatrics has issued guidelines for the use of IVIG in children with KD (73). Recently, however, Mason *et al.* examined the effects of IVIG on circulating immune complexes (CICs) in patients with CD (74). Although increased levels of CICs were noted, IVIG therapy did not appear to decrease their prevalence. Hence the authors concluded that CICs are not likely to be the primary immunopathologic mechanism of KD.

KD has been the subject of much clinical and basic research (75). Several investigators have focused on a possible infectious etiology. Until these issues are resolved, high-dose IVIG therapy instituted within 10 days after the onset of disease appears to reduce significantly the morbidity and mortality of associated cardiovascular complications (76).

Insulin-Dependent Diabetes Mellitus (IDDM)

Considerable evidence exists to support an autoimmune basis for IDDM or type I diabetes. In addition to the demonstration of islet cell-specific autoantibodies in serum during the onset of disease, postmortem examinations have also revealed coexisting infiltration of the islets of Langerhans with T lymphocytes (i.e., "insulinitis"). Recent studies have indicated that immunomodulatory agents such as cyclosporin A may retard progression of disease (77). In an uncontrolled clinical trial, six children with recently diagnosed IDDM were treated with high-dose IVIG for up to 6 months (78). Four children demonstrated a prolonged partial remission.

A larger, controlled trial of high-dose IVIG using 20 newly diagnosed patients, also treated for up to 6 months, further indicated that this form of therapy may be an adjunct to conventional treatment (79). Most significant was a difference in insulin requirements between the treated and the untreated patients, with the latter necessitating a larger maintenance dose than the former. Accompanying the decreased insulin requirement was a concomitant increase in serum C-peptide levels. No other immunologic parameters showed any differences between the treated and untreated groups.

These intriguing observations warrant further follow-up, as cyclosporin A is associated with serious side effects; perhaps combination therapy with high-dose IVIG may permit a dosage reduction of the former while retaining efficacy.

Bullous Pemphigoid

Bullous pemphigoid is a severe, autoimmune blistering disease secondary to autoantibodies which recognize antigens of the basement membrane. Conventional therapy for pemphigoid usually consists of steroids, immunosuppressive drugs, and/or plasmapheresis. Godard and colleagues described the treatment of 11 patients with bullous pemphigoid with IVIG (80). Rapid but transient responses were noted in eight patients, only one of whom had a prolonged remission. The authors speculate that combination therapy of IVIG with steroids may have a steroid-sparing effect.

PROPOSED MECHANISMS OF ACTION

While the rationale of IVIG replacement therapy for antibody deficiency states is obvious, its role as

an immunomodulating agent is less well understood. Several hypotheses have been evoked to explain the mechanisms by which IVIG may be effective in treating the numerous autoimmune disorders previously described. It is beyond the scope of this report to present these theories in detail. Rather, a brief summary of several currently popular propositions is described.

The efficacy of intact, native IgG as an immunomodulator is consistent with a model which suggests that unbound IgG, particularly when in excess, may compete with IgG complexed to antigens for Fc receptors on the surface of phagocytic cells in circulation and within the reticuloendothelial system. These cells are very effective in eliminating immune complexes (e.g., antibodies bound to cellular components such as RBCs, PMNs, platelets, hematopoietic stem cells, etc.) Thus blockage of Fc receptors with unbound IgG may inhibit destruction of autoantibody-bearing cells.

Jerne's network theory of immunoregulation is conceptually dependent upon the existence of naturally occurring antiidiotypic antibodies in circulation (81). Antiidiotypic antibodies specific for the idiotypes of various autoantibodies may be constitutively present in the serum of healthy individuals as a normal immunoregulatory mechanism. These antiidiotypic antibodies may selectively target plasma cells or other members of the B-lymphocyte lineage bearing membrane-bound autoantibodies for complement-dependent and/or cell-mediated cytotoxicity, thereby eliminating potential clones of autoantibody-producing cells.

The role of infectious agents has also been considered in the pathogenesis of some autoimmune reactions. Binding of antigens from etiologic agents to host cells may initiate an autoimmune response to the complex of neoantigen plus host-cell ("self") antigens. The elimination of the infectious agent with IVIG could thus break such a vicious cycle.

Support for one or several of the above proposals may be found in the literature. Only additional studies, both *in vivo* and *in vitro*, will define the mechanisms underlying the well-demonstrated immunomodulatory activities of IVIG.

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