Mechanisms of Disease

Intravenous Immune Globulin in Autoimmune and Inflammatory Diseases

Erwin W. Gelfand, M.D.

In an era in which new biologics are being introduced to target inflammation and autoimmunity, some older treatments persist. Immune globulin–replacement therapy has been a lifesaving treatment for patients with antibody deficiency. When immune globulin replacement was introduced in the 1950s for the treatment of primary immunodeficiency diseases, it was administered subcutaneously or by intramuscular injection; subsequently, preparations suitable for intravenous use were developed, and these have undergone progressive changes in composition, particularly the elimination of sugars and normalization of the salt content and osmolarity. As a result, reactions have become much less frequent. Intravenous immune globulin is prepared from plasma pooled from thousands of healthy donors. This pooling provides a diversity of antibody repertoires and antibody specificities. More than a dozen preparations suitable for intravenous administration have been approved by the Food and Drug Administration (FDA) for the treatment of primary immunodeficiency diseases.

The importance of regular immune globulin replacement in patients with antibody deficiencies was initially attributed to its ability to provide specific antibodies that could not be produced by these patients — in particular, antibodies to encapsulated organisms such as Streptococcus pneumoniae or Haemophilus influenzae. Since the introduction of immune globulin–replacement therapy administered on a regular basis, the incidence of severe infections such as meningitis, osteomyelitis, and lobar pneumonia has been substantially reduced. However, the therapeutic benefits may not be limited to antibody replacement; intravenous immune globulin may also play an active role in primary immunodeficiency diseases. Supporting this notion is the observation that the benefits do not necessarily correlate with actual antibody titers. Indeed, in patients with X-linked agammaglobulinemia who were infected with mycoplasma species, intravenous immune globulin was found to have considerable benefits, especially a reduction in isolates, even though antibody titers were virtually undetectable. This potential for benefits beyond those achieved by means of antibody replacement was first revealed when immune globulin was used to treat a patient with antibody deficiency in whom autoimmune thrombocytopenia developed. In the landmark description of this case by Imbach and colleagues, immune globulin replacement successfully restored platelet counts to the normal range. Since these initial observations were reported, the use of immune globulin in the treatment of inflammatory and autoimmune diseases (especially when it is administered intravenously) has expanded enormously. These diverse disorders now range from blistering skin diseases to transplant rejection, neurologic diseases, and a host of other inflammatory and autoimmune conditions. Given these apparent benefits in patients with disorders that often have no recognizable common cause, it is clear that immune globulin treatment has gone far beyond antibody replacement for the treatment of immunodeficiency states.
Currently, immune globulin is used in the treatment of a wide variety of diseases, with more than 75% of the intravenous immune globulin in the United States administered to patients with autoimmune or inflammatory conditions. At present, the FDA-approved indications for immune globulin therapy are limited (Table 1). A few years ago, chronic inflammatory demyelinating polyneuropathy was added to the list of indications, and the use of intravenous immune globulin is also now accepted for patients undergoing kidney transplantation when the recipient has a high antibody titer or when the donor’s blood is ABO-incompatible. Most recently, the FDA approved the use of immune globulin to treat patients with multifocal motor neuropathy. For each of these indications, double-blind, placebo-controlled trials have been conducted to establish the efficacy of intravenous immune globulin. The efficacy of all the brands of intravenous immune globulin available in the United States has been established for the treatment of primary immunodeficiency diseases, whereas for other indications, a limited number of controlled studies (often with a single product) have been performed. At present, there is a lack of comparative data to suggest that one brand is more effective than other brands. However, the various preparations of intravenous immune globulin may differ from one another in ways that may be important in a particular patient.

In the United States, intravenous immune globulin has often been used for off-label indications. A large number of diseases have shown potentially beneficial responses to intravenous immune globulin, and for many of these diseases, Medicare or a commercial insurer has approved reimbursement for such therapy, often conditionally, requiring documentation of contraindications to or a lack of response to conventional therapies (Table 1). For most of these indications, evidence is available from only small, controlled trials or from clinical experience with limited numbers of patients. According to these lines of evidence, there are a number of conditions for which intravenous immune globulin has not been considered medically necessary and would not be covered. For example, intravenous immune globulin has been used to treat autism and chronic fatigue syndrome, but its effectiveness in these conditions is unsubstantiated.

As an alternative to other therapies, the overall use of intravenous immune globulin continues to expand as novel insights are gained into the underlying pathophysiological characteristics of certain diseases and the need for immunomodulation. One area of growing interest is the potential use of intravenous immune globulin in patients with Alzheimer’s disease. Passive immunotherapy with the use of anti–beta amyloid (Aβ) antibodies was attempted (e.g., monoclonal antibodies such as bapineuzumab), but this approach had limited success. Recently, intravenous immune globulin, which contains naturally occurring antibodies, was shown to contain antibodies to Aβ peptides, and in both in vitro neuronal-cell cultures and an in vivo mouse model, intravenous human immune globulin had beneficial effects. Intravenous immune globulin promoted the recognition and removal of natively formed Aβ deposits by microglia. A recent 18-month, open-label, follow-up study of 24 patients with Alzheimer’s disease receiving intravenous immune globulin showed a reduction in ventricular enlargement on magnetic resonance imaging and an improvement in cognition scores. Larger controlled studies are needed to address the efficacy of intravenous immune globulin in Alzheimer’s disease.

The doses used in the treatment of autoimmune and inflammatory conditions are generally four to five times higher than those used for replacement therapy in patients with immunodeficiency disease. A total dose of 2 g per kilogram of body weight, administered over a period of 2 to 5 days on a monthly basis, is most often used and results in serum IgG levels of 2500 to 3500 mg per deciliter. The ways in which intravenous immune globulin exerts its immunomodulatory and anti-inflammatory effects remain unclear, with many pathways in the innate and adaptive immune systems being potentially targeted (Fig. 1). Since many of the diseases that respond to intravenous immune globulin therapy appear to have pathologic profiles that differ from one another, it has been difficult to develop a common mechanistic understanding of its mode of action.
Many distinct but non–mutually exclusive mechanisms have been suggested, as can be seen from studies of intravenous immune globulin as treatment for Kawasaki’s disease, a disease for which the effects of this intervention are dramatic. Although the underlying pathophysiological characteristics of the disease remain to be clearly defined, the antiinflammatory potential of intravenous immune globulin in patients with Kawasaki’s disease has been well described.11 After a single intravenous infusion of immune globulin, fever often abates, with concomitant reductions in several inflammatory markers.12 Among the many explanations for these effects are decreases in the production of proinflammatory cytokines (e.g., tumor necrosis factor α [TNF-α], interleukin-1α, and interleukin-6), the down-regulation of adhesion molecule and chemokine and chemokine-receptor expression, and the neutralization of superantigens.13,14 Indeed, antibodies to many of these proinflammatory cytokines and chemokines have been detected in intravenous immune globulin, and increases in serum antiinflammatory cytokines (e.g., interleukin-10) and receptors and antagonists (e.g., soluble TNF-α receptor and interleukin-1–receptor antagonist) have been observed after infusion of intravenous immune globulin.15–20 It is important to note that most of the studies of the mechanisms of action of intravenous immune globulin were carried out in vitro or in animal models.

One general mechanism of action potentially links the benefits of intravenous immune globulin to the response to glucocorticoids. In the majority of chronic inflammatory diseases in which intravenous immune globulin has been used, glucocorticoid therapy is generally considered to be the first-line treatment. The antiinflammatory effects of glucocorticoids are mediated through intracellular receptors that modulate (enhance or inhibit) gene expression.21 As a result, glucocorticoids can reduce inflammation at several levels, including modulation of cytokine and chemokine production, of adhesion-molecule expression, and of inflammatory-cell accumulation. The major glucocorticoid receptor, the alpha isoform of the glucocorticoid receptor (GRα), functions primarily as a ligand-activated transcription factor. Alternatively splicing of the glucocorticoid-receptor gene results in the expression of a GRβ isoform that does not bind ligand and may exhibit domi-

| Table 1. Diseases for Which Intravenous Immune Globulin Has Been Shown to Be Beneficial. |
|---|---|
| **FDA-approved indications** | **Primary immunodeficiency disease** |
| | **Chronic lymphocytic leukemia** |
| | **Pediatric HIV infection** |
| | **Kawasaki’s disease** |
| | **Allogeneic bone marrow transplantation** |
| | **Chronic inflammatory demyelinating polyneuropathy** |
| | **Kidney transplantation involving a recipient with a high antibody titer or an ABO-incompatible donor** |
| | **Multifocal motor neuropathy** |
| **Additional approved indications with criteria** | **Neuromuscular disorders** |
| | **Guillain–Barré syndrome** |
| | **Relapsing–remitting multiple sclerosis** |
| | **Myasthenia gravis** |
| | **Refractory polymyositis** |
| | **Polyradiculoneuropathy** |
| | **Lambert–Eaton myasthenic syndrome** |
| | **Opsoclonus–myoclonus** |
| | **Birdshot retinoathy** |
| | **Refractory dermatomyositis** |
| **Hematologic disorders** | **Autoimmune hemolytic anemia** |
| | **Severe anemia associated with parvovirus B19** |
| | **Autoimmune neutropenia** |
| | **Neonatal alloimmune thrombocytopenia** |
| | **HIV-associated thrombocytopenia** |
| | **Graft-versus-host disease** |
| | **Cytomegalovirus infection or interstitial pneumonia in patients undergoing bone marrow transplantation** |
| **Dermatologic disorders** | **Pemphigus vulgaris** |
| | **Pemphigus foliaceus** |
| | **Bullous pemphigoid** |
| | **Mucous-membrane (cicatricial) pemphigoid** |
| | **Epidermolysis bullosa acquisita** |
| | **Toxic epidermal necrolysis or Stevens–Johnson syndrome** |
| | **Necrotizing fasciitis** |

* This is an abbreviated list of conditions approved under Medicare Part D or Aetna Clinical Policy Bulletin (2012). Criteria include medical certainty of diagnosis, medical necessity owing to the failure of usual treatments, contraindications to usual treatments, rapid progression or relapse, documentation of progress, and attempts to adjust drug dosages without improvement. FDA denotes Food and Drug Administration, and HIV human immunodeficiency virus.
nant negative activity. Patients vary in their response to glucocorticoids, and their degree of sensitivity may vary with the stage of the disease. A reduced response to glucocorticoids or the need to increase the dose has been associated with increased GRβ expression, decreased glucocorticoid-receptor binding, or a decreased affinity for glucocorticoids. States of glucocorticoid resistance or insensitivity have been described in many autoimmune and inflammatory conditions, including asthma, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, and transplant rejection. Development of a “resistant state” may be induced by proinflammatory cytokines. In studies involving patients with severe, glucocorticoid-resistant asthma, treatment with intravenous immune globulin improved the response to glucocorticoids, as shown in vitro in assays of T-cell sensitivity but also in vivo with the normalization of glucocorticoid-receptor binding in association with improved clinical responses to glucocorticoid therapy after 3 to 6 months of treatment. Thus, intravenous immune globulin may play a major role in many of these disease states by improving glucocorticoid-receptor binding through mechanisms that remain to be defined but that may include suppression of pro-inflammatory cytokine production.

Nonetheless, despite the identification of immunomodulatory and antiinflammatory activities in various diseases, the benefits of immune globulin are not easily explained and probably cannot be explained by a uniform mechanism. The pleiotropic effects of intravenous immune globulin may provide advantages in treating the various inflammatory and autoimmune conditions. Several ac-
tivities appear to be clearer than others. Some of the beneficial effects of administered immune globulin extend beyond its half-life, implying that the results are not due simply to enhanced passive clearance or interference with pathogenic autoantibodies. Administered immune globulin can exert both antiinflammatory and proinflammatory effects, depending on the interacting partner (Fig. 2). Antiinflammatory activities are seen more generally when intravenous immune globulin is administered at relatively high doses, whereas proinflammatory activities involving complement activation or binding of IgG through the receptor (R) for the crystallizable fragment (Fc) portion of IgG (FcγR), particularly on innate immune effector cells, are seen at low doses. The relative expression levels and affinities of activating and inhibitory FcγRs that trigger counteracting signaling pathways may establish a balance or threshold for activation of immune effector cells. In turn, different cytokines and other proinflammatory or antiinflammatory stimuli can alter this balance and affect FcγR-mediated effector-cell functions such as phagocytosis, degranulation, release of proinflammatory cytokines, antibody-dependent cell cytotoxicity, and antigen presentation.27-29

Other mechanisms appear to be dependent on either the IgG antigen-binding fragment (Fab) or Fc (Fig. 1 and Table 2), and both fragments have been linked to the antiinflammatory or immunomodulatory activities of IgG.29,30 Since intravenous immune globulin contains many antibodies with distinct specificities, it has been suggested that its therapeutic benefits may be the result of antibody Fab binding to a variety of proteins or cell-surface receptors. These include binding to specific cytokines, cytokine receptors, Fas, sialic acid–binding Ig-like lectin-9 (Siglec-9), and CD5, among others.15-20,29,31,32 Other Fab-dependent mechanisms that have been reported involve the reestablishment of the idiotypic–anti-idiotypic network.33 Intravenous immune globulin contains an array of anti-idiotypic antibodies that can target B lymphocytes expressing these idiotypes and down-regulate or eliminate autoreactive clones. Although these activities may support the importance of the Fab fragment in the benefits of intravenous immune globulin, the evidence that implicates the Fc fragment as playing a central role is greater. Data from humans and from mouse models of several diseases, including immune thrombocytopenic purpura, nephrotic nephritis, and rheumatoid arthritis, have indicated that the Fc portion and intact IgG were essential to the activities in autoimmune diseases.34-36 The potential mechanisms for the Fc-mediated activity, in large part, reflect the various effector pathways, receptors, and ligands that can interact with the Fc portion of IgG. The most prominent among them include the complement pathway, the neonatal Fc receptor (FcRn), and activating and inhibitory Fc receptors for IgG (FcγRs) (Fig. 2).

REDUCTION OF COMPLEMENT UPTAKE

The binding of IgG to potentially harmful complement fragments (C3a, C3b, C4b, and C5a) blocks deposition of these fragments on target tissues, thus preventing subsequent immune damage that arises from cell destruction or aggravated inflammation.37 Increased uptake of complement has been shown in diseases such as active dermatomyositis, Kawasaki’s disease, autoimmune hemolytic anemia, the Guillain–Barré syndrome, and myasthenia gravis. After treatment with intravenous immune globulin, complement uptake was reduced.38 However, the importance of this mechanism of action has been questioned by studies showing that complement inactivation by cobra-venom factor has no effect on the activity of intravenous immune globulin.39

SATURATION OF FcRn

FcRn is a critical regulator of the half-life of IgG. Normally, IgG binds to FcRn, which is found on many tissues, including skin and muscle, and which is highly expressed on vascular endothelial cells. FcRn is a protective receptor that attenuates the catabolism of IgG, preventing its degradation by lysosomes and returning intact IgG to the circulation.40 One approach to blocking the activity of autoantibodies would be to intercept their interaction with this receptor. This would then shorten the half-life of the autoantibody, more rapidly eliminating it from the circulation, thereby reducing target-cell damage. Although the role of intravenous immune globulin–mediated FcRn saturation is an appealing concept,41,42 it has been difficult to validate in various experimental models.30

BLOCKADE OF ACTIVATING Fc RECEPTORS

In light of the importance of FcγRs in many antibody-directed effector functions, it is logical to assume that blocking activating FcγRs can limit
these pathologic events. This mechanism poses certain challenges, since the FcγRs in humans — FcγRIIA/B/C and FcγRIIIA (and their mouse counterparts, FcγRIIB, FcγRIII, and FcγRIV) — tend to be low- or medium-affinity receptors, and this limits their ability to interact with monomeric IgG. Monomeric IgG constitutes more than 95% of intravenous immune globulin. By extension, preparations of intravenous immune globulin that contain dimeric or multimeric IgG could be more antiinflammatory.\(^43\) In the presence of their respective antigens, the IgG antibodies in the preparation of immune globulin could create high levels of immune complexes and “outcompete” the autoantibody–antigen complex or block its access to activating FcγRs — mechanisms that have been suggested with respect to the immunomodulatory activities of anti-D immune globulin\(^44\) or hyperimmune serum.\(^45\)

**Regulation of FcγRIIB**

More closely linked to the antiinflammatory activity of intravenous immune globulin is the low-affinity inhibitory receptor FcγRIIB. Among genetically manipulated animals that did not express this receptor, those with immune thrombocytopenic purpura, rheumatoid arthritis, or nephrotoxic nephritis were no longer protected by intravenous immune globulin.\(^35,36,46-49\) An important attribute of intravenous immune globulin may be its ability to induce an increase in the expression of FcγRIIB on effector macrophages.\(^35,36,46\) This induction may explain the benefits seen with intravenous immune globulin in a study involving...
patients with chronic inflammatory demyelinating polyneuropathy; in these patients, as compared with a control group, inhibitory FcγRIIB expression was reduced on memory B cells. As with the low-affinity activating receptors, a direct interaction between intravenous immune globulin and the low-affinity, inhibitory FcγRIIB is unlikely, but modulation of effector macrophages through the up-regulation of inhibitory FcγRIIB may be important in reducing proinflammatory responses (Fig. 3).

**IMMUNOMODULATION BY SIALYLATED IgG**

Despite the many effects on various effector-cell types, cytokines, chemokines, and other mediators that have been ascribed to intravenous immune globulin and the potential for imbalance in activating and inhibitory FcγR expression levels, it remains unclear whether a single mechanism underlies the varied effects of this therapy in disparate diseases and why high doses of intravenous immune globulin are required for the antiinflammatory or immunomodulatory activities. Since the pathophysiological characteristics of many of the autoimmune and inflammatory diseases are only now being unraveled, it is also unclear whether the antiinflammatory activities of intravenous immune globulin seen in many of the mouse models of inflammatory disease may be replicated in humans.

Some insights can be gained from the observation that different patterns of IgG glycosylation can be detected in animal models of inflammation and in patients with rheumatoid arthritis or various forms of autoimmune vasculitis, supporting the concept that unique IgG glycoforms participate in the modulation of antibody effector function in vivo. This led to the discovery that a small, sialylated fraction of IgG was responsible for the antiinflammatory activities in a mouse model of arthritis. The glycan moiety is an integral part of the scaffold for FcγR binding. To define the role of the glycan structure on the Fc fragment of IgG in mediating the antiinflammatory activity, these carbohydrates were deleted. Deglycosylated intravenous immune globulin appeared to be unable to provide antiinflammatory protection in this model of rheumatoid arthritis. The antiinflammatory activity resided in a minor population of pooled IgG that contained terminal α-2,6 sialic acid linkages on their Fc-linked glycans. Notably, this fully processed glycan was found in only 1 to 3% of IgG in the intravenous immune globulin preparations, accounting for the equal effects seen with the infusion of low doses of sialylated Fc fragments and the doses of native intravenous immune globulin that were higher by a factor of 10. The need for glycosylation eliminates the possibility of a simple FcRn competition model, since FcRn, unlike other FcγRs, retains its affinity for deglycosylated Fc fragments. The loss of FcγR binding with deglycosylated IgG links the two effector molecules, IgG and FcγR.

However, a direct relationship between IgG and FcγR is doubtful, since there is evidence that sialic acid–rich IgG has a decreased affinity for classical FcγRs in humans and mice, which excludes the possibility that sialic acid–rich intravenous immune globulin blocks the access of autoantibody immune complexes to activating FcγRs. Together, the data are more likely to support the notion of a novel receptor on regulatory macrophages that specifically recognizes sialic acid–rich IgG and promotes an antiinflammatory environment (Fig. 3). In acute disease, in which significant reductions in terminal sialic acid residues in serum and autoantibodies have been observed, the administration of intravenous immune globulin could restore levels of sialic acid–rich IgG and thereby dampen inflammatory activity by increasing inhibitory FcγRIIB expression and suppressing the effector function of autoantibodies. To be effective, sialylated Fc

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**Table 2. Potential Antiinflammatory and Immunomodulatory Activities of IgG.**

<table>
<thead>
<tr>
<th>Fab-mediated activities</th>
<th>* Fab denotes antigen-binding fragment, Fc crystallizable fragment, FcγR receptor for the Fc portion of IgG, and FcRn neonatal Fc receptor.</th>
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<tbody>
<tr>
<td>Suppression or neutralization of autoantibodies</td>
<td>Suppression or neutralization of cytokines</td>
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<tr>
<td>Neutralization of activated complement components</td>
<td>Restoration of idiotypic–anti-idiotypic networks</td>
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<tr>
<td>Blockade of leukocyte-adhesion-molecule binding</td>
<td>Targeting of specific immune cell–surface receptors</td>
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<td>Modulation of maturation and function of dendritic cells</td>
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<th>Fc-dependent activities</th>
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<td>Blockade of the FcRn</td>
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<td>Blockade of activating FcγR</td>
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<tr>
<td>Up-regulation of inhibitory FcγRIIB</td>
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<td>Immunomodulation by sialylated IgG</td>
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fragments appeared to require SIGN-R1 (specific intercellular adhesion molecule 3 [ICAM-3]–grabbing nonintegrin-related 1), a specific C-type lectin expressed on macrophages. SIGN-R1 binds preferentially to α-2,6-sialylated Fc, suggesting that a specific binding site is created by the sialylation of Fc. In an animal model of immune thrombocytopenic purpura, amelioration of platelet phagocytosis mediated by intravenous immune globulin could be blocked with a SIGN-R1–specific antibody.

The studies in animals have provided important insights, but for many of the proposed activities, the mechanisms must be validated in humans. The models used may offer only limited insight into human disease, and the mechanism of action of intravenous immune globulin in the various models may not be consistent. This is perhaps best illustrated in some models of experimental arthritis or immune thrombocytopenic purpura, in which the importance of Fc sialylation for the activity of intravenous immune globulin was clearly shown. However, when such therapy was tested in another model of immune thrombocytopenic purpura, its effects appeared to be independent of sialylation of the Fc regions of intravenous immune globulin. Furthermore, although the human orthologue of SIGN-R1, dendritic-cell–specific ICAM 3–grabbing nonintegrin (DC-SIGN), exhibits binding specificity for sialylated Fc that is similar to that in animals, it differs in cellular distribution — a factor that may result in important species differences in the antiinflammatory protection provided by intravenous immune globulin.

Figure 3. Potential Model for Antiinflammatory Activity of Sialylated Fc.

Sialylated Fc, present in low quantities in intravenous immune globulin, binds to SIGN-R1 on macrophages, resulting in the release of soluble mediators. These mediators bind to effector macrophages and increase expression of the inhibitory FcγRIIB receptors, which compete with antigen–antibody complex binding to activating FcγRs. The net result is an increase in the concentration of the complexes required to initiate an inflammatory response.

The use of intravenous immune globulin has been firmly established for the treatment of a wide va-
riety of autoimmune and inflammatory diseases, either as adjunctive therapy or as first-line therapy in some conditions, such as Kawasaki’s disease. Its use has generated novel and important insights into the complexities of the immune system and has highlighted the importance of a native molecule, IgG, as a key regulator of both innate and adaptive immunity. These informative studies have not been without challenges. Results in animal models have not been entirely consistent and easy to translate to human disease. Double-blind, placebo-controlled trials remain essential to establish the efficacy of this intervention in a variety of disease states. As with many interventions, there may be specific subgroups of patients with certain diseases who are more likely to benefit from treatment with intravenous immune globulin. Some of the variability in the development and clinical manifestations of a disease, and ultimately the response to intravenous immune globulin, may relate to differential antibody Fc glycosylation patterns or may be explained by genetic and functional variations in FcγR expression.

Intravenous immune globulin therapy, especially at doses of 2 g per kilogram per month, is expensive, and with expanding use there are concerns about present and future supplies, especially if the donor pool decreases or is limited by safety issues and increased pathogen screening of donors of the source plasma. Attempts to bioengineer a protein with immunomodulatory activities similar to those of native IgG should be a priority if we are to sustain this approach to disease modification. Delineation of the potential role of sialylated Fc in some of the immunomodulatory activities may be one important step if results similar to those shown in animals can be found in humans. If only a portion of the total intravenous immune globulin is effective, that would explain why the doses currently required are so high. The successes with intravenous immune globulin witnessed over the past few decades are just the beginning. Now the real work needs to begin.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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