

Minireview

Utility of Intravenous Immune Globulin in Kidney Transplantation: Efficacy, Safety, and Cost Implications

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Intravenous immunoglobulin preparations (IVIG) are known to be effective in the treatment of various autoimmune and inflammatory disorders into their immunomodulatory, immunoregulatory, and anti-inflammatory properties. Recently, IVIG has been utilized in the management of highly sensitized patients awaiting renal transplantation. The mechanisms of suppression of panel reactive antibodies (PRA) in patients awaiting transplantation are currently under investigation and appear to be related to anti-idiotypic antibodies present in IVIG preparations. In this review, the various immunomodulatory mechanisms attributable to IVIG and their efficacy in reducing PRAs will be described. In addition, the use of IVIG in solid organ transplant recipients will be reviewed. The adverse events, safety considerations, and economic impact of IVIG protocols for patients awaiting solid organ transplantation will be discussed.

Key words: IVIG, kidney transplantation, panel reactive antibodies

Received 29 October 2002, revised 12 December 2002 and accepted for publication 21 January 2003

Introduction

Currently 52 000 patients with end stage renal disease (ESRD) are awaiting renal transplantation in the US (1). Of these patients, greater than 30% are considered highly sensitized to human leukocyte antigens (HLA), with an anti-HLA panel reactive antibody (PRA) greater than 30% (1). Development of high antibody levels usually results

from multiple blood transfusions, previous failed transplants, and pregnancies (2). Patients with elevated anti-HLA antibodies often wait extended periods of time for a compatible organ. Transplantation of incompatible organs with positive antibody crossmatches usually results in severe rejection and allograft loss (3, 4). Currently, there are few options for improving the odds of successful transplantation for a highly sensitized patient. Thus, these patients wait extended periods of time on dialysis with attendant morbidities and mortality (5, 6). As a result, there is a need to find therapies that can control or abrogate the production of alloantibodies in a predictable and safe manner.

Previous approaches for management of these patients have included plasma exchange, and protein A immunoabsorption combined with cytotoxic drug therapies. These methods are associated with high risk of infection and a rebound in antibody formation (7, 8). Other methods such as plasmapheresis alone or cyclophosphamide therapy are not reliable methods to reduce excess antibody titer levels (9). Protein A immunoabsorption allow the removal of IgG from serum. Although this treatment removes IgG subclasses 1, 2 and 4, it does not remove IgG subclass 3, which contains the complement activating antibodies with the greatest ability to cause inflammation and injury.

Intravenous immune globulins (IVIG) have potent immunomodulatory functions and have shown benefit in the treatment of a variety of autoimmune and inflammatory disorders (10–13). Intravenous immune globulins could represent an answer for the highly sensitized individual in that it may combine immuno-inhibitory effects on anti-HLA alloantibody synthesis and potentially provide immuno-protective effects, improving transplant and patient survival (4,14,15). Currently available data suggests that IVIG alone or in combination with plasma exchange may offer a new, more effective approach to the management of the highly sensitized patient. This review will discuss the role of IVIG in transplantation of the highly sensitized patient. It will also compare the commercially available IVIG preparations and review the adverse events associated with administration of these products. Lastly, we will discuss the economic impact of improving transplantability of these patients.

Intravenous immune globulins

Intravenous immune globulins are commercially prepared preparations from IgG derived from pooled human plasma of 50 000–100 000 or more screened donors (13,16). Therefore, it is likely that IVIG contains the entire compilation of antibodies found in normal human serum. Autoantibodies can be detected in normal individuals and patients with autoimmune disease. The etiology is unknown but could result from cross reactivity with viral or bacterial antigens or a lack of the deletion mechanism for autoreactive T cells or B cells (13). The IVIG products are comprised of > 90% intact IgG, few dimers or aggregates, little F (ab')₂ fragment, and traces of IgM and IgA (17). Intravenous immune globulins contain antibodies to: Cardiolipin, T-cell receptor idiotypes, CD4, CD5, CD40, CD95, HLA class I, HLA class II-DR, Rh D antigen, IL-1 α , IL-4, IL-6, TNF- α GM-CSF, IL-1 β , IFN- γ receptor (18). The beneficial effects of IVIG often persist past the infused half-life, suggesting that IVIG triggers a mechanism(s), which could result in long-term suppression of the synthesis of autoantibodies, possibly including anti-HLA antibodies (4,19,20). Intravenous immune globulins also induce IgM blocking antibodies that appear to have the ability to down-regulate anti-HLA antibody activity and possibly synthesis (4,9).

In the preparation of IVIG products, several methods have been employed to reduce side-effects associated with aggregation of IgG that can concomitantly activate immune cells. These include: proteolytic cleavage, enzymatic treatment by pepsin, plasmin degradation, chemical treatment via alkylation/reduction or sulphonation (16, 21). The products are made free of vasoactive contaminants, isohemagglutinins, and undergo viral inactivation steps (21). These processes all significantly reduced the IgG yield from plasma. Other methods to keep the IgG molecules from aggregation include polyethylene glycol (PEG), ion exchange (DEAE sepharose column) chromatography, glycine addition and acidification with pepsin with the addition of sucrose as a stabilizer (16, 22).

There are a large number of suggested mechanisms by which IVIG exerts its immunomodulatory effects (Table 1). The mechanisms of action of IVIG are diverse and may vary in the context of one disease compared with another. Intravenous immune globulins act on several components of the immune system through the F (ab')₂ fragment, which has two antigen-binding sites, or through the Fc fragment, which binds complement and can bind to Fc receptors on immune cells (Table 2).

Although IVIG has multiple mechanisms of action that could be of benefit in modulating undesirable alloimmune responses, the most potentially important seem to be reduction of alloantibodies through anti-idiotypic circuits, inhibition of inflammatory cytokine generation (23, 24), inhibition of complement-mediated injury, and inhibition of antibody production (13, 23).

Table 1: Mechanism of immune modulation by intravenous immunoglobulin preparations (17)

Inhibition of complement-mediated injury
Inhibition of circulating immune complex injury
Reversal of T-cell activation in Kawasaki disease
Increase in suppressor cells in idiopathic thrombocytopenic purpura
Reduced T-cell proliferation
Reduced phagocytosis
Reduced reticular endothelial system clearance of immune complexes
Reduction of NK cell function
Reduced spontaneous Ig secretion <i>in vitro</i> in HIV and autoimmunity
Induction of the Fc γ R1IB receptor on macrophages
Inhibition of B-cell development and autoantibody production.
Inhibition of pathogenic antibody by anti-idiotypic antibodies

IVIG = intravenous immunoglobulin preparations; NK = natural killer.

Table 2: Mechanisms of action of intravenous immune globulin in autoimmune and alloimmune disorders (13)

B cells and antibodies
Control of emergent bone marrow B-cell repertoires
Negative signaling through Fc receptors
Selective down-regulation and up-regulation of antibody production
Neutralization of circulating autoantibodies and alloantibodies by anti-idiotypes
T cells
Regulation of production of helper T-cell cytokines
Neutralization of T-cell superantigens
Cell growth
Inhibition of lymphocyte proliferation
Regulation of apoptosis
Fc receptors
Blockade of Fc receptors on macrophages and effector cells
Induction of antidependent cellular cytotoxicity
Induction of inhibitory Fc receptor
Inflammation
Attenuation of compliment-mediated damage
Decrease in immune-complex mediated inflammation
Induction of anti-inflammatory cytokines
Inhibition of activation of endothelial cells
Neutralization of microbial toxins
Reduction of corticosteroid requirements

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Mechanism of action of IVIG in patients with elevated PRAs

Fc-receptor-mediated effects

IgG molecules bind by way of their Fc region to Fc γ receptors on macrophages, neutrophils, eosinophils, platelets, mast cells, natural killer cells, and B cells (25). The Fc region of the antibody interacts with hematopoietic cells to disable or up-regulate cellular activities depending

on the Fc γ receptor types. Treatment of idiopathic thrombocytopenic purpura and other autoantibody-induced cytopenias by IVIG is mediated by the blockade of the Fc γ receptor on macrophages, which prevents the removal of sensitized platelets by the reticuloendothelial system (13, 26). Recently, it has been demonstrated that IVIG interacts with Fc γ receptor IIB, which is a negative signaling receptor on B cells (27). Potentially, anti-idiotypic antibodies in IVIG bind to the B-cell receptor and crosslink up-regulated Fc γ IIB. This results in a negative signal to the B cell with cessation of proliferation and probable induction of apoptosis (27, 28). Thus, long-term elimination of anti-HLA producing B cells could be accomplished via crosslinking B-cell receptors specific for HLA antigens with induced Fc γ IIB. The crosslinking could induce inhibition of these B cells or deletion through apoptosis. This hypothesis remains to be proven.

B cells and antibodies

The ability of IVIG to neutralize autoantibodies possibly results from the presence of anti-idiotypic antibodies against autoantibodies (and alloantibodies). An immediate effect could be mediated through blocking autoantibodies and eliminating them. Anti-idiotypic antibodies in IVIG could neutralize pathogenic autoantibodies in a similar manner to natural autoantibodies, and may serve as a humoral component that regulates autoreactivity of antibodies in plasma (13).

Another potentially important mechanism of action of IVIG is the ability to regulate CD19 expression on B cells. Data from Poe et al. (29) show that CD19-deficient animals [CD19 (-/-)] fail to develop normal B-cell activation while those that overexpress CD19 show uncontrolled B-cell antibody production and autoimmunity. Recent data from our lab (30) shows that IVIG significantly inhibits the expression of CD19 on activated human B cells. Theoretically, this reduction of CD19 expression could result in two important inhibitory mechanisms. First, CD19 acts as a complement receptor that allows for B-cell activation after complement fragments are bound. Intravenous immune globulins would interfere with this in two ways: first, by absorption of C3b and second by reducing the expression of CD19 on B cells. Thus, it would appear that IVIG has the ability to induce the expression of a negative regulatory receptor (Fc γ IIB) on immune cells and to inhibit or decrease the expression of a positive costimulatory molecule (CD19). The highly sensitized patient with persistently elevated anti-HLA antibodies may be unable to down-regulate these responses as a result of defective regulatory pathways. Thus, IVIG potentially offers a source of passively administered regulatory anti-idiotypic antibodies that has the potential to 'realign' a dysfunctional immune response. It is important to note that these are potential mechanisms of action that have not been demonstrated in humans. However, the persistence of the beneficial effects generated by IVIG in many patients suggests that cellular regulatory mechanisms are induced.

Complement activation

Pooled immune globulin preparations have potent anti-inflammatory activities. One important way in which immune globulins reduce inflammation is through interference with the generation of the membrane-attack complex (C5b-C9) and the resulting complement-mediated tissue damage. IgG binds activated components C3b and C4b, thereby preventing fragment deposition on target surfaces (13). Intravenous immune globulins also prevent complement-induced damage by accelerating the conversion of C3b to its inactive form, iC3b (31). Several studies have shown that immune globulin can be effective in treating allograft rejection episodes. This may be through interference with complement-mediated injury to the allograft by alloantibody (20, 32, 33). Wassmuth *et al.* showed that various immune globulin products inhibited the cytotoxicity of anti-HLA antibodies *in vitro* through scavenging activated complement components (14). These investigators felt that the inhibitory effects of immune globulins on cytotoxicity assays were mediated solely through inhibition of complement. In an elegant study performed in a xenotransplant model (pig to baboon or cynomolgus monkey heart transplant), Magee et al. (34) showed that human IVIG could significantly extend the survival of these xenografts from 30 min to 10 days. This beneficial effect was clearly shown to be through inhibition of complement-mediated injury. Recent data by Pratt et al. (35) also suggest that the local synthesis of complement in the transplanted kidney is critical for T-cell and B-cell activation and may represent the bridge between the innate and adaptive immune response to an allograft. These investigators showed that kidneys from C3-deficient [C3 (-/-)] mice had significantly improved survival with minimal rejection when compared with wild-type kidneys [C3 (+/+)]. The authors suggest that C3b plays a critical role in activating T cells through the CR1/CR2 complement receptors. Thus, the ability of IVIG to inhibit C3-mediated injury through absorption of C3b may be critical to its ability to inhibit antibody-mediated injury of allografts and subsequent T-cell activation.

T cells and cytokines

Intravenous immune globulins may contain several factors in addition to IgG, including IgA, solubilized membrane products, and HLA determinants, which can interfere with the communication between T cells and antigen-presenting cells (36,37). Several studies have found that solubilized CD4, CD8, HLA Class I and Class II determinants can block the interactions that occur in T-cell mediated cytotoxicity (38). Intravenous immune globulins induce changes in T-cell suppressor activity in patients receiving IVIG for common variable immunodeficiency (39). Intravenous immune globulins decrease the ability of antigen-reactive T cells to produce IL-1, IL-2, and interferon- γ (13). The ability of IVIG to bind to activated T-cell receptors may inhibit blast transformation (40,41). Intravenous immune globulins also have the ability to inhibit the mixed lymphocyte response in sensitized renal transplant candidates *in vitro* (8,42).

Intravenous immune globulins can modulate proinflammatory cytokines (43). Intravenous immune globulins produce a dose-dependent decrease in IL-6 production (23,24) and IVIG suppresses TNF- α and IL-2 synthesis (44). Intravenous immune globulins inhibits antigen-stimulated T-cell proliferation, mediated by the regulation of IL-2 and IL-4 production (45). Other possible cytokine interactions include reducing IL-1 secretion by monocytes, blocking the activity of IL-1 or enhancing the production of IL-1 receptor antagonist by triggering Fc receptors on macrophages (46,47).

IVIG for the treatment of acute rejection

Although an infrequent occurrence, steroid-resistant rejections pose a significant complication in renal transplant recipients. Several centers have published their experience using IVIG for the treatment of severe or resistant rejection episodes.

We have previously published the results of 10 transplant recipients (seven kidney and three heart) with severe allograft rejection who received high-dose IVIG (2 g/kg as a single dose). All three cardiac patients had severe humoral-vascular rejection requiring inotropic support and aortic balloon pump for circulatory support. All patients had been treated with steroids and antilymphocyte preparations without resolution. Most patients responded well to IVIG with resolution of their rejection episodes. Results of protein G column fractionation studies from two patients showed induction of blocking IgM and IgG antibodies in these patients by IVIG infusion, suggesting this as a possible mechanism for long-term reduction in alloimmune responses. Another important observation from this experience was the lack of recurrent rejection episodes in most patients (20).

The University of Pittsburgh published results of 17 patients treated with IVIG for biopsy-proven acute rejections. Thirteen were treated for steroid-resistant rejection and four had antilymphocyte antibody-resistant rejection. Time to IVIG treatment was 17.5 ± 23.7 months post-transplant and IVIG was administered for a total dose of 2 g/kg over 2–10 days, according to the fluid status of the patient. Ten patients also had their steroids recycled and seven had mycophenolate mofetil (MMF) added to their regimen. After IVIG therapy, 9/17 demonstrated complete resolution of rejection, and five additional patients demonstrated reduced rejection severity. In a subgroup of seven patients that received IVIG monotherapy without MMF or steroid recycle, six demonstrated reduction or resolution of rejection (32).

Casadei et al. (48) conducted a randomized study of 30 patients with steroid resistant rejection, half of which were treated with IVIG 500 mg/kg for 7 days and half received OKT3 5 mg/day for 14 days. Rejection was

reversed in 73% of the IVIG group and 87% of the OKT3 group ($p = ns$). Two-year patient and graft survival were not different in the groups. Intravenous immune globulin was as effective in reversing acute steroid resistant rejection as OKT3 but without OKT3's adverse event profile (48).

Thus, IVIG appears to be an important addition to the antirejection therapeutic armamentarium. Further studies will be necessary to define which patients would benefit most from this therapy. However, those with steroid or antibody-resistant forms of rejection have a high rate of reversal with IVIG, suggesting that IVIG inhibits different pathways than our standard anti-T-cell therapies.

Treatment of highly HLA sensitized patients with IVIG

Montgomery et al. (49) from Johns Hopkins University utilized plasmapheresis and IVIG to remove donor-specific, anti-HLA antibody, in two protocols: (1) rescuing patients with established acute humoral rejection (AHR) and (2) preemptively desensitizing recipients who had a positive crossmatch against a potential living donor (Table 3). Three patients received plasmapheresis/IVIG for AHR rescue and four were treated for a positive crossmatch.

Patients with AHR underwent plasmapheresis every other day. A 100-mg/kg dose of IVIG or Cytogam[®] (CMV hyperimmune globulin, Medimmune Inc. Gaithersburg, MD) was given after each plasmapheresis. The IVIG/plasmapheresis therapy was discontinued as clinical improvement was seen or donor-specific antibodies were no longer detectable.

Patients treated in the preemptive group received plasmapheresis/IVIG therapy pretransplant until a crossmatch negative status was achieved. All patients in this group received the therapy at least two additional times post-transplant because all patients in this group developed antibody-mediated rejection. Patients also received pulse steroid therapy (methylprednisolone 500 mg/day \times three doses) followed by a gradual steroid taper before or during plasmapheresis/IVIG therapy.

Immunosuppression consisted of triple therapy with tacrolimus, MMF, and prednisone. Three preemptive patients also received five doses of daclizumab and three were started on tacrolimus and MMF at the start of IVIG/plasmapheresis therapy with prednisone initiated at the time of transplant.

All seven patients had functioning grafts at 57.7 ± 39.9 weeks follow up. The four preemptive patients required between one and six plasmapheresis/IVIG treatments to obtain a negative crossmatch. All four patients in this group also experienced a single episode of AHR,

Table 3: Summary of protocols involving immune globulin for sensitized patients

Center	Johns Hopkins (49)	University of Maryland (50)	Hôpital Européen Georges Pompidou (51)	Cedars-Sinai (52)
Desensitization protocol	PP/IVIG until crossmatch (-) MP 500 mg/day × 3 doses	MMF prior to PP, IVIG 500 mg/kg over 7 days, TAC, and CS started with first PP treatment. PP TIW × 2 weeks before transplant	IVIG 2g/kg over 48 h × 3 doses at 4-week intervals	IVIG 2g/kg (140 g max) × 1 dose for LD IVIG 2g/kg (140 g max) × 4 doses for CAD
No. of patients treated	4	15	15	48
No. of patients transplanted	4	11	13	44 (16 CAD; 28 LD)
Acute rejection (%)	100%	36.4%	7.7%	29%
Graft loss (%)	0%	0%	15.4% (2)	6.8% (3)
Infection/malignancy (%)	N/A	9.1%	23.1%	0%
Follow-up period (months)	10 (4.3–17)	13.3 ± 2.4 (3–26)	12	24
Serum creatinine (mg/dL)	1.0 (0.8–1.2)	1.6 ± 0.2 (1.1–2.4)	NA	1.4 + 0.5 (0.4–2.0)

LD = live donor; TAC = tacrolimus; CAD = cadaveric; CS = corticosteroids; PP = plasmapheresis; TIW = three times per week
IVIG = intravenous immune globulin; MP = methylprednisolone.

which meant that the IVIG/plasmapheresis therapy needed to be started again to reverse the episodes. HLA class I-specific antibody was present in 6/7 patients (49).

Schweitzer et al. (50) from University of Maryland also established a protocol to reduce high PRA to allow for live donor (LD) kidney transplantation. Fifteen patients who had positive antihuman globulin (AHG) crossmatches against their donors completed the study (Table 3). Mean peak PRA prior to treatment for the groups was 69%. Two diabetic patients required a cadaver pancreas transplant following the living donor kidney (SPLK).

Study participants were treated with a standard dose of MMF 3 days before the first plasmapheresis. Patients were also on standard doses of tacrolimus and prednisone on the first day of plasmapheresis. All three immunosuppressive drugs were continued post-transplant. Intravenous immune globulin (500 mg/kg over 7 days) was started after the first plasmapheresis. The patients received 10 days of OKT3 at the time of transplant, dosed to keep the percentage of CD3-positive lymphocytes less than 5%. Before transplant, patients received six treatments of plasmapheresis, three times weekly.

Four of 15 patients remained crossmatch positive after the six plasmapheresis treatments, all four remained on dialysis and no transplant was performed. The remaining 11 became AHG crossmatch-negative and underwent the LD transplantation, two of which also received a simultaneous cadaver pancreas. Immediately post transplant, three patients required at least one dialysis, the longest period of delayed graft function being 13 days. All 11 patients are now dialysis free with a mean follow-up of 13.3 months and mean SCr of 1.6 mg/dL.

Of the 11 patients transplanted, only four biopsies in four different patients showed signs of acute rejection. Three of these biopsies had a mild neutrophilic vascular infiltrate interpreted as possible antibody-mediated rejection. These three were successfully reversed with additional plasmapheresis, OKT3 or antithymocyte globulin, and IVIG. The fourth biopsy was a mild cellular rejection on postoperative day 41, which was treated with pulse steroids. Immunologic monitoring demonstrated that the protocol resulted in a reduction in antibody titers. Both of the SPLK transplants failed as a result of accelerated chronic rejection and early thrombosis, possibly caused by an alloantibody-mediated response.

Plasmapheresis was well tolerated in general. No plasmapheresis treatments had to be stopped early because of adverse reactions. This desensitization protocol allowed 11 patients to receive transplants that would not otherwise have been carried out because of positive crossmatches, and few rejections were seen (50).

Recently Glotz and colleagues published a report on 15 highly sensitized patients who received IVIG prior to

kidney transplantation (51). Eleven of the patients were second transplants and the mean time on dialysis was more than 9 years. Three courses of IVIG were given at 4-week intervals, each course consisting of 2 g/kg given over 48 h. The post-transplantation immunosuppression regimen consisted of Thymoglobulin® (Sangstat, Fremont, CA) for 10 days, tacrolimus, MMF, and steroids. Of the 15 patients treated with IVIG, 13 (87%) were desensitized, with an 80% mean reduction of the PRA levels, and transplanted. Two patients did not experience a change in the anti-HLA antibodies and therefore were not transplanted. Eleven patients received a cadaveric kidney transplant, while two received a living donor transplant. Two grafts were lost, one as a result of thrombosis and the other because of rejection. One patient died with a functioning graft 15 months post-transplant as a result of a stroke. Lastly, another patient with a history of acute lymphocytic leukemia and bone marrow transplantation, developed post-transplant lymphoproliferative disorder 6 months after the kidney transplant and died. This small series demonstrates that repeated doses of 2 g/kg led to transplantation in 80% of this highly sensitized population.

Cedar-Sinai Protocol for desensitization

We have previously presented our protocol to utilize IVIG to decrease crossmatch positivity and allow for living donor and cadaveric transplantation (52). Patients first undergo a standard T-cell cytotoxicity assay against a random panel of 50 donors to determine PRA. If positive, we then assess the potential utility of IVIG by adding IVIG to the assay in a 1 : 1 dilution. In many cases, the cytotoxicity of these antibodies is completely blocked through anti-idiotypic antibodies present in the IVIG. This *in vitro* assay gives us some idea of the expected efficacy of IVIG *in vivo*. We have adapted this assay to single donor-recipient pairs (Figure 1). Those patients who demonstrate *in vitro* inhibition of donor-specific cytotoxicity with IVIG receive IVIG 2 g/kg (maximum 140 g) while on dialysis. The crossmatch is repeated, and if it is negative, a living donor

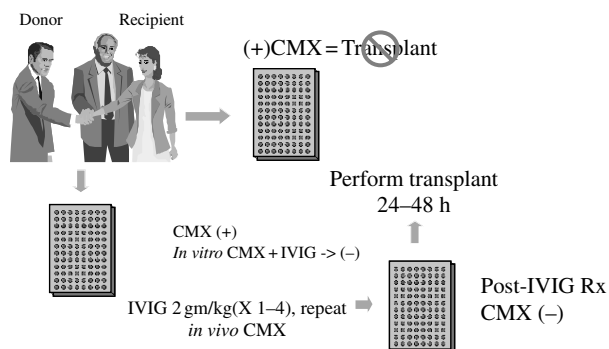


Figure 1: Cedars-Sinai intravenous immune globulin protocol for panel reactive antibodies (PRA) reduction and transplantation.

transplant is performed. Patients waiting for a cadaveric transplant who do not have living donors are offered the protocol if they have been on the UNOS list for 5 years and have received frequent cadaver kidney offers where consistently positive crossmatches are seen. These patients receive 2 g/kg of IVIG on dialysis monthly \times 4. The idea is to modulate anti-HLA antibody levels and find a crossmatch negative kidney. We have transplanted 44 patients using this approach. There are 28 living donor recipients and 16 cadaver recipients. Of the 16 cadaver recipients, 13 were kidneys, one kidney/heart, one kidney/liver, and one heart. The cadaver recipients with an average PRA of 83% had been on the waiting list for > 5 years and often had incompatible cross-matches with multiple potential donors. Nearly all patients had specific antibodies to donor antigens.

The incidence of acute rejection was 29%, with only four patients requiring OKT3. The patient and graft survival at 2 years is 97.5% and 89.1%, respectively. Three grafts were lost to rejection. The mean SCr values at 2 years are 1.4 mg/dL. From this work we conclude that the *in vitro* IVIG crossmatch test can predict the *in vivo* clinical response to IVIG therapy. In addition, long-term clinical outcomes have been excellent for most patients. Thus, it appears that IVIG alone offers significant benefits in desensitizing highly HLA-sensitized patients and allowing for successful transplantation in patients previously thought to be untransplantable.

Adverse events related to IVIG administration

The incidence of adverse events related to IVIG administration ranges from 12% to 23% (53). The most common infusion-related reactions include headache, fever, fatigue, chills, myalgias, dizziness, hypotension, sweating, nasal congestion, wheezing, chest tightness, abdominal pain, and nausea. These occur more often with rapid infusions (\geq 0.8 mL/kg/min), and may be mediated by increased levels of inflammatory cytokines and vasoactive substances (54). These symptoms are self-limiting and usually respond to slowing or interrupting the infusion or treatment with nonsteroidal anti-inflammatory drugs. More severe and generally delayed reactions include severe headache and aseptic meningitis (55). These are infrequent but are more common in patients with a history of migraine headaches. These usually respond to analgesics. Skin reactions such as urticaria, pruritus, and petechiae occur rarely.

Severe anaphylactic transfusion reactions may occur in patients with complete IgA deficiency who developed anti-IgA antibodies of the IgG and perhaps IgE isotypes (56). These reactions are extremely rare, estimated as 1 in 20 000–47 000 transfusions (57) or 1.3 reactions per million units of blood or blood products transfused (58).

Treatment of infusion-related adverse events include: (1) slowing or stopping the infusion; (2) treatment with diphen-

hydramine, ibuprofen, and/or corticosteroids; (3) administration of intravenous fluids; (4) epinephrine treatment; (5) diazepam therapy for muscle spasms; and (6) consideration of testing for anti IgA antibodies. If the patient requires multiple infusions, the next infusion should be administered more slowly and consideration should be given to changing IVIG products, as some reactions are product specific.

Renal dysfunction or acute renal failure has been associated with administration of IVIG (59–62). The primary associated cause of renal failure is sucrose found in some IVIG products (63). The FDA received 88 reports of cases in the US from 1995 to 1998 occurring within 7 days of IVIG infusion (64). Ninety percent of the recipients received a sucrose-containing compound and 7% received maltose or glucose-containing IVIG products. The indications for IVIG administration in this series was hematologic (46%), autoimmune/immunologic (23%), neurologic (17%), and infectious causes (11%) (64). Acute renal failure can be avoided by reducing the osmolarity of sucrose-containing products. This is accomplished by reconstituting lyophilized products in sterile water instead of saline and limiting the concentration of IVIG (and sucrose) to 9% and the amount of IVIG given to a maximum of 140 g at one infusion (The Carimune[®] product can be reconstituted to a 9% concentration in sterile water, Jordan, unpublished observation).

More recently, serious thrombotic events have been linked to the administration of IVIG products. On March 26, 2002, the Food Drug Administration (FDA) website posted Dear Doctor letters released by two manufacturers of IVIG regarding thrombotic events associated with infusion of the Gammagard[®] S/D and Polygam[®] S/D products (65). The letter cites 28 articles that have previously reported thrombotic events such as myocardial infarction, deep vein thrombosis, central retinal vein occlusion, vasculitis, cerebral vasospasm, stroke, and pulmonary embolism. Rapid infusion of IVIG has been identified as a possible risk factor for the development of thrombosis. The companies recommend, 'In all patients with thrombotic risk factors such as coronary disease, diabetes mellitus . . . the infusion concentration for these patients should be no more than 5%. The infusion rate should be initiated no faster than 0.5 mL/kg/h and increased slowly only if well tolerated to a maximum rate of 4 mL/kg/h'. It is important to emphasize that this complication is not true for all IVIG products and appears to possibly be related to the sodium content and osmolarity of specific IVIG products. From our observations, the incidence of side-effects is likely to increase in those products with high sodium content (1–2%) and high osmolarity (i.e. > 500 milliosmols/L) (Jordan, unpublished observation). It is very important to know the products that pharmacies dispense and what concentrations, sodium content and osmolarity are being infused. Again reconstituting lyophilized products in sterile water instead of saline and limiting the concentration of IVIG (and sucrose) to 5–9% will provide a low osmolarity

product with low sodium content and help prevent many of the more serious side-effect experiences with IVIG.

Comparison of IVIG products

There are many components or factors present in IVIG aside from IgG, including: sugars, salt, albumin, polyethylene glycol, traces of endotoxin, and pepsin, other nonimmune globulin blood proteins (haptoglobulins, LDL, HDL, etc.), platelet-activating factor (PAF), and coagulation factor XI. Products also vary in their osmolarity and salt content (Table 4). Osmolarity ranges between 192 and 1250 milliosmols depending on the product, immune globulin concentration, and differences in the salt and sugar concentrations. The osmolarity of the product must be considered when treating patients with renal dysfunction who may not tolerate such a large osmotic load. The concentration of sugar may influence the choice of products in diabetic patients. The sodium chloride (NaCl) content ranges between 0 and 2% and low-salt formulations are available for patients who are fluid and/or salt sensitive. Higher IVIG concentration products may be advisable in patients with heart failure who may not tolerate excess fluid volume.

Economic impact of IVIG treatment protocols: consideration of reimbursement strategies

UNOS data indicates that patients with elevated PRAs are less likely to receive a transplant. Less than 10% of all transplants performed in 1998 had a PRA > 20% (Figure 2). Those with PRAs >30% have double the waiting time

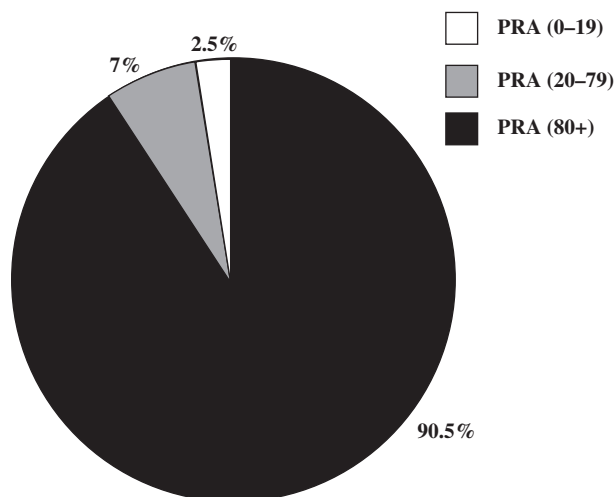


Figure 2: Number of transplants performed by panel reactive antibody (PRA) status (UNOS 1998). Of the transplants performed in 1998, less than 10% had elevated PRA levels.

before transplantation (1). Patients with an elevated PRA, who receive a transplant from a living donor or cadaver source, have a significantly shorter graft half-life (Figure 3) (66,67). Data from the Johns Hopkins Medical Center estimates that 28% of the blood type O patients on the waiting list have living donors who are ABO incompatible (ABOI) (McEwan R, MBA, personal communication, April 26, 2002) and may also benefit from antibody-lowering protocols with IVIG and/or plasmapheresis.

Medicare approval and subsequent funding is the first obstacle for antibody-lowering protocols because it applies

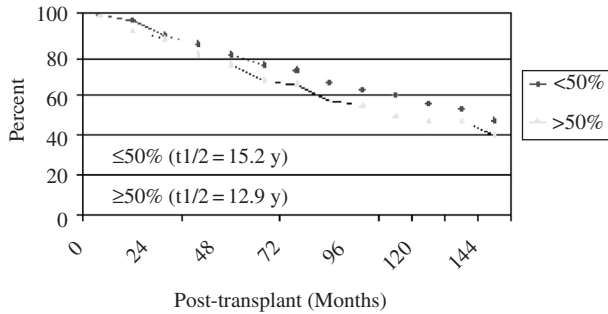
Table 4: Diluent, sugar, sodium content, and osmolarity (66)

Product	IVIG concentration	Diluent	Sugar	Sodium	Osmolarity (Osmol/L)
Gamimune N	5%	10% maltose	10% maltose	Trace	305
Gamimune N	10%	Glycine	None	Trace	274
Carimune ¹	3%	0.9% NaCl	2.5% sucrose	0.9%	489
Carimune	3%	Sterile water	2.5% sucrose	0%	192
Carimune	6%	0.9% NaCl	5% sucrose	0.9%	690
Carimune	6%	Sterile water	5% sucrose	0%	384
Carimune	12%	0.9% NaCl	10% sucrose	0.9%	1074
Carimune	12%	Sterile water	10% sucrose	0%	768
Gammagard/Polygam	5%	Sterile water	2% glucose	1%	636
Gammagard/Polygam	10%	Sterile water	4% glucose	2%	1250
Venoglobulin-I	5%	Sterile water	2% mannitol	0.5%	253
Venoglobulin-I	10%	Sterile water	4% mannitol	1%	670
Venoglobulin-S	5%	D-sorbitol	5% sorbitol	unknown	300
Iveegam	5%	Sterile water	5% glucose	0.3%	373
Gammar-IV	5%	Sterile water	5% sucrose	0.5%	330
Gammar-IV	10%	Sterile water	10% sucrose	1%	699
Cytogam	5%	Sterile water	5% sucrose	0.05%	> 200

¹Previously Sandoglobulin

Adapted with permission from UHC Technology Assessment: Intravenous Immunoglobulin Preparations, April 1995. IVIG = intravenous immune globulin.

Graft survival by PRA status: Living-donor recipients 1988–98



Graft survival by PRA status: Cadaver recipients 1988–98

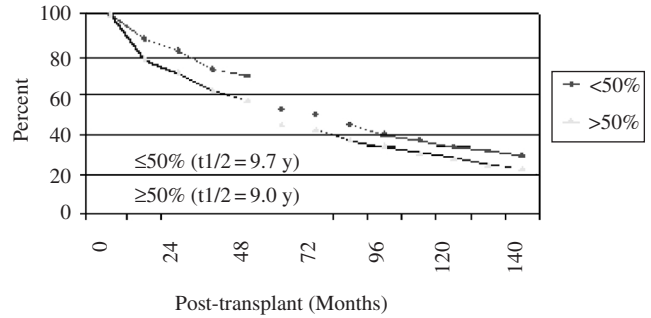


Figure 3: Graft survival in living donor and cadaveric recipients by panel reactive antibody status. Patients with an elevated panel reactive antibody (PRA) at the time of transplant have shorter graft half-lives. *USRDS Renal Data Systems 2001 Annual Report.*

to so many of the potential eligible candidates. Another reason to gain approval of the procedure by Medicare is that the primary carriers generally follow the lead of Medicare and will likely consider paying for a procedure if covered by Medicare. Coverage by private carriers can be accomplished by being persistent in demonstrating excellent outcome data and by contrasting costs that are incurred if the patient is transplanted vs. remaining on dialysis.

Four states (Delaware, Maryland, Texas, and Virginia) and the District of Columbia have approved IVIG (CytoGam) for use both pre- and post-transplant and issued specific J codes for each indication. When pursuing coverage in your local areas meet with your Medical Director of your Medicare Intermediary and discuss the scientific evidence supporting the use of IVIG in highly sensitized patients and

discuss the method of documentation to support payment of these procedures.

When assessing the financial benefits of IVIG therapy the following must be determined: (1) what are the costs of IVIG protocols (with or without plasmapheresis)? (2) What are the numbers of potential candidates who are highly sensitized? (3) What are the costs associated with positive crossmatches? (4) What is the cost associated with ESRD (dialysis access, complications, infections, peripheral vascular disease, cardiovascular disease other inpatient factors)? (5) What are the quality of life issues?

Table 5 lists the billing recommendation for the various IVIG treatment procedures and how it may be billed based on its proximity to the transplant. The third column is left blank for each site to enter their specific cost data.

Table 5: Suggested billing for each phase of transplantation

Line item	Proximity to transplant	Billing recommendation	Institution cost for IVIG protocol
Line placement for plasmapheresis ¹	Pre	Standard billing	
Plasmapheresis ¹	Pre/Post	APC	
Tacrolimus	Pre	Drug card	
Mycophenolate mofetil	Pre	Drug card	
Albumin	Pre/Post	APC (part of PP)	
IVIG	Pre/Post	APC + J code	
Isoagglutinin titer	Pre/Post	KAC (TT)	
Flow crossmatch	Pre/Post	KAC (TT)	
Daclizumab induction	At	DRG	
Penicillin	At	DRG	
Patient stay within driving distance	Post	NA	
Biopsies	Post	APC	
Clinic visits (follow up)	Post	Standard billing	

¹If required.

APC = ambulatory payment classification; KAC = kidney acquisition center; DRG = diagnosis related group; IVIG = intravenous immune globulin.

Table 6: Annual costs of medicare end stage renal disease patients

Medicare payments per patient year for dialysis patients	\$53 412
Medicare payments per patient year for transplant and post transplant coverage	\$17 091

Costs based on the USRDS 2001 Annual Report, 1995–99 Medicare Claims data.

The average cost for 140g of IVIG at Cedars-Sinai is approximately \$6500, while Johns Hopkins average cost for CytoGam at 100 mg/kg for approximately six doses is \$12 000. This data can be compared with the annual cost incurred by Medicare for care of ESRD patients and renal transplant recipients (Table 6) (67). When the annual costs of patients transplanted with antibody-lowering protocols are compared with those without antibody-lowering protocols (Table 7) (McEwan R, MBA, personal communication, April 26, 2002), the cost associated with the antibody-lowering protocol is substantially less than maintaining patients on dialysis for 4–5 years. What are the national implications to Medicare? When transplanting the eligible 12 000 plus patients on the waiting list who have a PRA > 30% or are potential ABOI recipients, the cumulative savings to Medicare exceeds one billion dollars (Table 8) (McEwan R, MBA, personal communication, April 26, 2002).

Summary

Currently 30–40% of the patients placed on the renal transplant list are highly sensitized, with PRAs > 30%.

This problem continues to grow, as treatment options for these patients are limited. Several centers are implementing protocols utilizing intravenous immune globulin with initial success. The mechanisms of IVIG involved in reduction of antibody levels are multifactorial and complex, including interactions at the FcγIIb receptor on B cells, modulation of the idiotype–anti-idiotype interaction, inhibition of cytokine gene activation, and inhibition of T-cell activation. Regardless of the mechanism, pretreatment with IVIG successfully allows transplantation in an otherwise untransplantable population. The result of IVIG or plasmapheresis/IVIG treatment enhances quality of life for end-stage renal patients and decreases the economic burden on the healthcare system.

Acknowledgments

The authors would like to thank Brigitte Reeb of The Comprehensive Transplant Center, Johns Hopkins Hospital, for her assistance with the financial data and Sony Tuteja, PharmD, of the Cincinnati Transplant Institute for her assistance in preparation of this manuscript

Table 7: Patient cost comparison

	Patients transplanted with antibody lowering therapy	ESRD patients without antibody lowering therapy	
		PRA > 30%	Blood type O
Wait time on UNOS list (years)	1	5.1	4.3
Per patient cost during wait time (dialysis, inpatient, outpatient, etc.)	\$53 412	\$269 731	\$229 672
Transplant care (\$17 091/year for 36 months)	\$51 273	\$51 273	\$51 273
Antibody lowering protocol (avg) ¹	\$35 540	–	–
Total cost per patient	\$140 225	\$321 004	\$280 945

¹Johns Hopkins costs; each institution should substitute center cost based on Table 4.

Table 8: Medicare exposure comparison

	ESRD patients without Antibody lowering therapy		Patients eligible for Antibody lowering therapy
	PRA > 30%	Blood Type O	
Patients eligible for sensitization ¹	5 000	7 678	12 678
% patients medicare primary at time of transplant	57%	57%	48%
Total Medicare patients	2 850	4 377	5 452
Total cost per patient	\$321 004	\$280 945	\$140 225
Total medicare exposure	\$914 860 260	+ \$1 229 568 426	– \$764 451 844
	= \$1 379 976 842 savings to Medicare		

¹Assumes 50% of patients with PRA > 30 and 28% of the ABOI wait list patients able to find living donors.

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