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

Stanley Jordan, Charlotte Cunningham-Rundles, and Robert McEwan

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 antiidiotypic 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

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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 deletional 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 idotypes, CD4, CD5, CD40, CD95, HLA class I, HLA class II-DR, Rh D antigen, IL-1α, IL-4, IL-6, TNF-α GM-CSF, IL-1β, 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, isohemagglutins, 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)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of complement-mediated injury</td>
<td>Inhibition of pathogenic antibody by anti-idiotypic antibodies</td>
</tr>
<tr>
<td>Inhibition of circulating immune complex injury</td>
<td>Induction of Fc receptor-mediated effects</td>
</tr>
<tr>
<td>Reversal of T-cell activation in Kawasaki disease</td>
<td>Neutralization of microbial toxins</td>
</tr>
<tr>
<td>Increase in suppressor cells in idiopathic thrombocytopenic purpura</td>
<td>Inhibition of activation of endothelial cells</td>
</tr>
<tr>
<td>Reduced T-cell proliferation</td>
<td>Neutralization of autoantibodies by anti-idiotypic antibodies</td>
</tr>
<tr>
<td>Reduced phagocytosis</td>
<td>Regulation of production of helper T-cell cytokines</td>
</tr>
<tr>
<td>Reduced reticular endothelial system clearance of immune complexes</td>
<td>Regulation of apoptosis</td>
</tr>
<tr>
<td>Reduction of NK cell function</td>
<td>Inhibition of T-cell activation in Kawasaki disease</td>
</tr>
<tr>
<td>Reduced spontaneous Ig secretion in vitro in HIV and autoimmune</td>
<td>Attenuation of complement-mediated damage</td>
</tr>
<tr>
<td>Induction of the FcγRIIB receptor on macrophages</td>
<td>Decrease in immune-complex mediated inflammation</td>
</tr>
<tr>
<td>Inhibition of B-cell development and autoantibody production.</td>
<td>Induction of antidependent cellular cytotoxicity</td>
</tr>
<tr>
<td>Inhibition of pathogenic antibody by anti-idiotypic antibodies</td>
<td>Induction of inhibitory Fc receptor</td>
</tr>
<tr>
<td>IVIG = intravenous immunoglobulin preparations; NK = natural killer.</td>
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</tr>
</tbody>
</table>

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 complement-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 Fcγ 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 Fcγ receptor types. Treatment of idiopathic thrombocytopenic purpura and other autoantibody-induced cyto-
penias by IVIG is mediated by the blockade of the Fcγ receptor on macrophages, which prevents the removal of
sensitized platelets by the reticuloendothelial system (13, 26). Recently, it has been demonstrated that IVIG inter-
acts with Fcγ receptor IIB, which is a negative signaling
receptor on B cells (27). Potentially, anti-idiotypic anti-
bodies in IVIG bind to the B-cell receptor and crosslink up-regulated Fcγ 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 elimina-
tion of anti-HLA producing B cells could be accomplished
via crosslinking B-cell receptors specific for HLA antigens
with induced Fcγ 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. Antiidiotypic antibodies in IVIG could neu-
tralize pathogenic autoantibodies in a similar manner to nat-
ural 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. Theoretic-
ally, 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 (Fcγ IIB) on immune cells and to inhibit
or decrease the expression of a positive costimulatory
molecule (CD19). The highly sensitized patient with per-
sistently 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 anti-
bodies 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-
flammatory 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 prevent-
ing 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 ep-i-
sodes. 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 pro-
ducts 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 sur-
vival of these xenografts from 30 min to 10 days. This ben-e-
ficial 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 activa-
tion and may represent the bridge between the innate and
adaptive immune response to an allograft. These investiga-
tors 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 absorp-
tion 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 determin-
ants 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 IL-4 production (45). 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.

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 allo-raft 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 hyper-immune 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 x 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

<table>
<thead>
<tr>
<th>Center</th>
<th>Johns Hopkins (49)</th>
<th>University of Maryland (50)</th>
<th>Hôpital Européen Georges Pompidou (51)</th>
<th>Cedars-Sinai (52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desensitization protocol</td>
<td>PP/IVIG until crossmatch (–)</td>
<td>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.</td>
<td>IVIG 2 g/kg over 48 h × 3 doses at 4-week intervals</td>
<td>IVIG 2 g/kg (140 g max) × 1 dose for LD IVIG 2 g/kg (140 g max) × 4 doses for CAD</td>
</tr>
<tr>
<td>No. of patients treated</td>
<td>4</td>
<td>15</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>No. of patients transplanted</td>
<td>4</td>
<td>11</td>
<td>13</td>
<td>44 (16 CAD; 28 LD)</td>
</tr>
<tr>
<td>Acute rejection (%)</td>
<td>100%</td>
<td>36.4%</td>
<td>7.7%</td>
<td>29%</td>
</tr>
<tr>
<td>Graft loss (%)</td>
<td>0%</td>
<td>0%</td>
<td>15.4% (2)</td>
<td>6.8% (3)</td>
</tr>
<tr>
<td>Infection/malignancy (%)</td>
<td>N/A</td>
<td>9.1%</td>
<td>23.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>10 (4.3–17)</td>
<td>13.3 ± 2.4 (3–26)</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 (0.8–1.2)</td>
<td>1.6 ± 0.2 (1.1–2.4)</td>
<td>NA</td>
<td>1.4 ± 0.5 (0.4–2.0)</td>
</tr>
</tbody>
</table>

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.](image-url)
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 × 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, myalgia, dizziness, hypotension, sweating, nasal congestion, wheezing, chest tightness, abdominal pain, and nausea. These occur more often with rapid infusions (≥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 diphenhydramine, 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 Polymagam® 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 osmolality (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 (haptoglobinins, 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 before transplantation (1). Patients with an elevated PRA, who receive a transplant from a living donor or cadaver source, have a significantly shorter 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 before transplantation (1). Patients with an elevated PRA, who receive a transplant from a living donor or cadaver source, have a significantly shorter 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

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

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

1Previously Sandoglobulin
Adapted with permission from UHC Technology Assessment: Intravenous Immunoglobulin Preparations, April 1995.
IVIG = intravenous immune globulin.
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

<table>
<thead>
<tr>
<th>Line item</th>
<th>Proximity to transplant</th>
<th>Billing recommendation</th>
<th>Institution cost for IVIG protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line placement for plasmapheresis¹</td>
<td>Pre</td>
<td>Standard billing</td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis¹</td>
<td>Pre/Post</td>
<td>APC</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Pre</td>
<td>Drug card</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Pre</td>
<td>Drug card</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Pre/Post</td>
<td>APC (part of PP)</td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td>Pre/Post</td>
<td>APC + J code</td>
<td></td>
</tr>
<tr>
<td>Isoagglutinin titer</td>
<td>Pre/Post</td>
<td>KAC (IT)</td>
<td></td>
</tr>
<tr>
<td>Flow crossmatch</td>
<td>Pre/Post</td>
<td>KAC (IT)</td>
<td></td>
</tr>
<tr>
<td>Daclizumab induction</td>
<td>At</td>
<td>DRG</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>At</td>
<td>DRG</td>
<td></td>
</tr>
<tr>
<td>Patient stay within driving distance</td>
<td>Post</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Biopsies</td>
<td>Post</td>
<td>APC</td>
<td></td>
</tr>
<tr>
<td>Clinic visits (follow up)</td>
<td>Post</td>
<td>Standard billing</td>
<td></td>
</tr>
</tbody>
</table>

¹If required.

APC = ambulatory payment classification; KAC = kidney acquisition center; DRG = diagnosis related group; IVIG = intravenous immune globulin.
The average cost for 140 g 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 FcγRIIB receptor on B cells, modulation of the idotype–anti-idotype 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 6: Annual costs of medicare end stage renal disease patients

<table>
<thead>
<tr>
<th></th>
<th>Medicare payments per patient year for dialysis patients</th>
<th>Medicare payments per patient year for transplant and post transplant coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD patients without antibody lowering therapy</td>
<td>$53 412</td>
<td>$17 091</td>
</tr>
</tbody>
</table>


### Table 7: Patient cost comparison

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

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

### Table 8: Medicare exposure comparison

<table>
<thead>
<tr>
<th></th>
<th>ESRD patients without Antibody lowering therapy</th>
<th>Patients eligible for Antibody lowering therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA &gt; 30%</td>
<td>Blood type O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients eligible for sensitization</td>
<td>5 000</td>
<td>12 678</td>
</tr>
<tr>
<td>% patients medicare primary at</td>
<td>57%</td>
<td>48%</td>
</tr>
<tr>
<td>time of transplant</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Total Medicare patients</td>
<td>2 850</td>
<td>5 452</td>
</tr>
<tr>
<td>Total cost per patient</td>
<td>$321 004</td>
<td>$140 225</td>
</tr>
<tr>
<td>Total medicare exposure</td>
<td>$914 860 260</td>
<td>–$764 451 844</td>
</tr>
<tr>
<td></td>
<td>+ $1 229 568 426</td>
<td></td>
</tr>
</tbody>
</table>

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