USE OF INTRAVENOUS IMMUNOGLOBULIN TO PREVENT OR TREAT INFECTIONS IN PERSONS WITH IMMUNE DEFICIENCY

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KEY WORDS: intravenous immunoglobulin, clinical use, immune deficiency, efficacy, safety

ABSTRACT
Intravenous immunoglobulin (IVIG) concentrates were originally developed as replacement therapy for individuals with primary deficiencies of the immune system. However, in various well-designed, controlled clinical trials, the ability of IVIG to prevent and possibly treat infections in patients with secondary immune deficiencies has also been considered. In this review, we briefly consider these different applications and suggest whether the data are sufficient to employ IVIG in these clinical settings.

Introduction
Concentrated preparations of immunoglobulins that can only be administered intramuscularly have been available since the early 1950s. Because only a small amount of immunoglobulin could be given by this route, and because of...
the discomfort associated with such injections, alternative approaches were
required. Modification of these intramuscular preparations using proteolytic
enzymes, like pepsin or papain, resulted in an intravenous immunoglobulin
preparation termed IVIG (1). Further modifications allowed production of
intact immunoglobulin (Ig) concentrates (2) with a normal distribution of the
IgG subclasses and pharmacokinetic features of native IgG (3). Although there
are some differences in the concentrations of other immunoglobulins, particu-
larly IgA (4), and of specific antibody titers, IVIG products are reasonably
similar.

In this review, we consider the use of IVIG to prevent and treat infections,
especially in those persons with immune deficiency.

Immune Deficiency

Immune deficiency syndromes are characterized by abnormal immune re-
sponses, especially B-cell responses (5). Persons with immune deficiency and
hypogammaglobulinemia are at increased risk of respiratory and urinary tract
infections, otitis media, and gastroenteritis. Common pathogens include Pneu-
mococcus sp. and Haemophilus influenzae for respiratory infections and Cam-
pylobacter sp., rotavirus, or Giardia sp. for gastrointestinal infections (1, 6–8).

Initial clinical trials with IVIG focused on persons with immune deficiency
(9–15). Although none of the studies was randomized or double-blind, results
suggested that IVIG, when given regularly, may prevent bacterial infections in
these persons. Dose and timing of IVIG infusions varied, but most data sug-
gested that a dose of ≥150 mg/kg was needed at a frequency of about every
four weeks. Other data suggest that dose and schedule should be tailored to
specific subjects because of individual variations in IgG catabolism (16–19).
One strategy is to give an initial dose of 200–400 mg/kg every four weeks,
with monitoring of the peak (immediate postinfusion) and trough (immediate
preinfusion) IgG levels for a minimum of three months. Dose and frequency
should be adjusted to maintain a peak less than 1500–2000 mg/dl and a trough
of more than 500 mg/dl.

Some data suggest that low levels of specific IgG subclasses (with normal
levels of other of these subclasses) are associated with frequent infections (20,
21). Rare patients with a normal total IgG serum concentration but extremely
low levels of IgG2, IgG4, or both have been reported (22, 23). There have been
several trials of IVIG to prevent infections in these patients (20, 21, 24–27).
Results were variable. Because imbalances in IgG subclasses can normalize
over time, especially in children (28), efficacy of IVIG in this setting is
controversial. Interestingly, pharmacokinetics of different IgG subclasses in
the infused IVIG is similar to that from corresponding native IgG molecules
(29).
Neonates

The immune system is not completely developed at birth. Consequently, normal newborns have low levels of immunoglobulins. These levels are even further depressed in premature neonates, where infections, particularly those caused by group B streptococci, are common (30–33).

Data from uncontrolled studies of IVIG indicated that IVIG decreases infections in premature neonates (34–37). Doses of 100 kg to 500 mg/kg given just after birth with subsequent frequent doses for the first several weeks of life seemed most effective.

Several large, randomized, placebo-controlled studies have also been reported (38–42). One study of 588 premature neonates reported a marked decrease in bacterial infections (particularly from gram-positive organisms) in neonates receiving IVIG at a dose of 500 mg/kg beginning about day 3 of life for about five doses over the next 7–8 weeks (41). In contrast, one large study of about 2000 premature neonates showed no benefit from IVIG (42). Because of these contradictory data, the 1992 National Institutes of Health Consensus Conference on IVIG did not recommend IVIG use in neonates (43). Some recent data suggest that differences in response to IVIG may correlate with antibody levels to pathogens like *Staphylococcus epidermidis*. This needs to be confirmed.

Burns

Persons with burns have decreased levels of immunoglobulins. Not surprisingly, bacterial infections are common in this situation, particularly those caused by *Pseudomonas aeruginosa* and *Escherichia coli* (44, 45).

Data on IVIG efficacy in burned persons are contradictory (46–48). A large, randomized trial showed no benefit (Hyland Division, Baxter Healthcare, personal communication). These results may stem from the complexity of burns and the difficulty in maintaining adequate immunoglobulin levels.

Surgery and Trauma

Although patients undergoing major surgery or exposed to serious trauma are not always immune compromised, they are at substantial risk for bacterial infections.

Two controlled studies comparing low- and high-dose IVIG therapy in persons with severe trauma undergoing abdominal or thoracic surgery suggested a benefit from IVIG in preventing infections (49, 50). Another uncontrolled trial showed no overall benefit, but only a subset of patients responded (51).

The largest and best designed study was in 352 high-risk surgical patients (52). The three-arm design included standard IVIG, a hyperimmune IVIG
[with high-titer antibody to the core lipopolysaccharide (endotoxin) of the cell wall common to gram-negative bacteria], and placebo. IVIG was given at a dose of 400 mg/kg immediately postsurgery and weekly thereafter for up to four doses. Persons receiving IVIG had significantly fewer gram-negative pneumonias and fewer days in the ICU and the hospital. There was no benefit in the hyperimmune IVIG group. These data suggest that prophylactic IVIG may be useful in high-risk surgery patients.

It is interesting to note that the initial study of passive immunotherapy in this setting using a hyperimmune plasma was promising (53), but subsequent hyperimmune globulins, including the one noted above, did not bear this out (54–57).

**B-Cell Cancer**

B-cell cancers are tumors of the antibody-producing cells, including chronic lymphocytic leukemia (CLL) and multiple myeloma. Patients with CLL often have hypogammaglobulinemia and/or frequent severe bacterial infections. Persons with multiple myeloma have increased levels of immunoglobulins, but their antibody responses are impaired and infections are common (58). Over a third of these individuals die from severe infection (59).

Two trials studied the effect of IVIG to prevent infections in patients with CLL (60) and multiple myeloma (61). Subjects were randomized to receive 400 mg of IVIG per kg or placebo monthly for one year. Both studies showed substantial reductions in severe bacterial infections in persons receiving IVIG. The actuarial probability of remaining infection free was also higher. Patients at the highest infection risk benefited most from IVIG prophylaxis (62, 63). These tended to be individuals who failed to respond immunologically to a test vaccination with Pneumovax®, the polyvalent pneumococcal vaccine. In CLL, a second study reported that 250 mg/kg per month produced similar results (64). Other, smaller studies have reported similar findings (65, 66). Cost-effectiveness of IVIG in the setting of CLL and multiple myeloma is controversial (67, 68).

**Transplantation**

Patients receiving transplants are also immune deficient and have increased risks of cytomegalovirus (CMV) and bacterial infections. Bone marrow transplant recipients are also at risk of developing graft-versus-host disease (GVHD).

Several studies focused on the efficacy of IVIG in bone marrow transplant recipients (69–74). These data suggest that IVIG does not prevent CMV infection but reduces the risk of CMV pneumonia and death. The incidence of acute GVHD is also reduced by IVIG. The effectiveness of IVIG is correlated with
the CMV state of the donor, recipient, and blood transfusions given posttransplant.

In contrast, IVIG is probably ineffective in bone marrow transplant with CMV infections (75–77). Some efficacy has been reported with IVIG combined with ganciclovir (78,79), but results are nevertheless poor.

IVIG prophylaxis also appears beneficial in reducing CMV infections and/or complications in recipients of kidney (80–82) and heart transplants (83–88).

**AIDS**

There are no antibodies to human immunodeficiency virus (HIV) in IVIG. However, because antibody responses are impaired in patients with acquired immunodeficiency syndrome (AIDS), IVIG may prevent infection.

In children with AIDS, prevention of bacterial infections by regular IVIG infusions (typically 400 mg/kg monthly) has been reported (89–91). A recent large, controlled trial confirmed these results (92). Data in adults are less convincing; randomized trials have not been reported (93–97).

Of recent interest are the data on HIV hyperimmune plasmas produced from relatively healthy HIV-infected donors. One large, controlled study reported a benefit (98–101).

**Safety**

Duhem and colleagues recently summarized potential adverse effects of IVIG (102). Acute reactions range from chills, nausea, flushing, chest pain, headache, and hypertension to serious anaphylactic reactions and, rarely, aseptic meningitis, hemolysis, and thrombosis. Most of the former are managed by decreasing the infusion rate or by premedication with corticosteroids (103).

In addition, there is a risk of transmission of blood-borne infections with IVIG. Although there are no reports of HIV or hepatitis B infection transmitted by IVIG therapy, sporadic hepatitis C transmission has been reported (102, 104–112). Recent advances in viral inactivation technology, particularly solvent-detergent treatment, have substantially reduced infection risk from these preparations.

In summary, considerable data support the notion of passive immune therapy with IVIG in immune-compromised patients.

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