

Intravenous Immunoglobulin: Striving for Appropriate Use

Arvind Kumar Suzanne S. Teuber M. Eric Gershwin

Division of Rheumatology, Allergy and Clinical Immunology, Department of Internal Medicine,
University of California at Davis School of Medicine, Davis, Calif., USA

Key Words

Immunoglobulin · Intravenous immunoglobulin ·
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Abstract

Background: Intravenous immunoglobulin (IVIG) is the mainstay therapy in human immune deficiency states characterized by qualitative and quantitative reductions in B cells. In addition, however, there is widespread use of IVIG in a number of other areas, including neuroimmunologic, infectious, dermatologic, hematologic, autoimmune, inflammatory and idiopathic disorders. In many of these cases, there are little objective data to support the use. **Methods:** We performed a review of more than 400 publications in PubMed using the key words 'intravenous immunoglobulin' and excluded publications that focused on immune deficiency, for which the indication for IVIG is already clear. **Results:** For a number of off-label indications, there is significant evidence of efficacy and IVIG has become the standard of care for many clinical syndromes other than immune deficiency. In some conditions, however, the data have not been well controlled or randomized and are often limited to case reports that are difficult to interpret. Although the critical shortage of IVIG of the last decade is no longer an issue, IVIG is expensive and not without risk. The use of IVIG should be based not only on clinical data, but also, and especially, on the biological rationale for its use. **Conclusions:** The ap-

propriate use of IVIG is an important issue that is difficult to resolve, and will continue to challenge clinicians based on expense and potentially limited supply, including the intrinsic limitations of donor plasma. The establishment of national and international voluntary registries to report use of IVIG in disorders for which evidence is lacking would be a first step toward facilitating randomized, controlled clinical trials.

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Introduction

Immunoglobulin products have been used as antibody replacement therapy in primary immunodeficiencies since the 1950s. Initially, intramuscular administration was used, followed in the 1960s and 1970s by chemically treated intravenous preparations whose use was limited by significant side effects and the short half-life of the immunoglobulin [1]. Intravenous immunoglobulin (IVIG) is a blood product prepared by separating the γ -globulin fraction from the plasma pooled from 3,000 to >60,000 human donors. For current products, donor plasma is screened for evidence of hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), and IVIG undergoes steps to inactivate known and unknown viruses. Alcohol fractionation followed by various anti-aggregation and stabilization measures (that vary by specific IVIG

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Correspondence to: Dr. M. Eric Gershwin, Division of Rheumatology
Allergy and Clinical Immunology, University of California at Davis School of Medicine
451 East Health Sciences Drive, Suite 6510
Davis, CA 95616 (USA)
Tel. +1 530 752 2884, Fax +1 530 752 4669, E-Mail megershwin@ucdavis.edu

Table 1. FDA-approved indications for IVIG products currently marketed in the United States

IVIG product (manufacturer/distributor)	Indication					
	primary immuno- deficiencies	CLL	ITP	Kawasaki syndrome	pediatric HIV type 1 infection	HSCT
Carimune NF (ZLB-Behring)	X		X			
Flebogamma 5% (Grifols Biologicals)	X					
Gamimune N 10%	X		X		X	X
Gammagard S/D (Baxter)	X	X	X	X		
Gammar-P IV (ZLB-Behring)	X					
Gamunex 10% (Bayer)	X		X			
Iveegam EN (Baxter)	X			X		
Octagam 5% (Octapharma)	X					
Panglobulin NF (ZLB/US Red Cross)	X					
Polygam S/D (Baxter Healthcare/American Red Cross)	X	X	X	X		

Extracted from IVIG product package inserts and from Schleis and Siegel [93]. CLL = CLL with hypogammaglobulinemia and/or recurrent bacterial infections; HSCT = hematopoietic stem-cell transplantation (allogenic) age $\geq$ 20 years.

product) results in a solution that is 95–99% IgG, with traces of IgA, IgM, IgE, and IgD [2]. The intravenous route allows larger doses of immunoglobulin to be administered while avoiding the pain often experienced when receiving large volumes of immunoglobulin intramuscularly. IVIG was first licensed for clinical use in the United States in 1981, when Imbach et al. [3] used high-dose IVIG to treat idiopathic thrombocytopenic purpura (ITP). Throughout the 1980s, IVIG was widely utilized to prevent or minimize infections due to primary immunodeficiency states. There are only six United States Food and Drug Administration (FDA)-approved indications for IVIG (table 1). These indications reflect evidence of efficacy of IVIG in these primary immunodeficiency and secondary immunodeficiency states and in the Kawasaki syndrome [4]. Even for these FDA-approved indications, the quality of evidence is variable. The last 2 decades have been marked by use of IVIG in a growing number of other areas, including neuroimmunologic, infectious, dermatologic, hematologic, autoimmune, inflammatory, and idiopathic disorders [4]. Off-label use exceeds FDA-approved labeled use by some reports [5]. For some of these off-label indications, there is significant evidence of efficacy and IVIG has become the standard of care, but in many situations the data are limited to case reports, small case series, expert opinion, or small trials that may not be well controlled, randomized, or blinded. In some of these

areas, IVIG treatment is used based on suspicion that a condition may have an autoimmune etiology or as a treatment of last resort when other efforts have failed. Although the critical shortage of IVIG supply of the late 1990s is no longer a major problem, IVIG is an extremely expensive treatment that is not without risk. As IVIG use continues to grow and since there are finite amounts of IVIG that can be produced based on intrinsic limitations of donor plasma, we will likely once again face issues of limited supply and increasing costs [6]. Such potential supply shortages may be most detrimental for patients with humoral immunodeficiencies for which there are currently no alternative therapies and for which alternatives are unlikely to be devised in the near future [7]. These issues make defining the most appropriate use of IVIG a matter of importance. To better characterize appropriate use, this article will review the major uses of IVIG today and consider the types of evidence that exist for these indications.

FDA-Approved Indications

Primary Immunodeficiency

As mentioned above, IVIG is the mainstay of treatment in patients with primary immunodeficiency with hypogammaglobulinemia (IgG <400 mg/dl), and there is

currently no effective alternative therapy in persistent disease. Its use has grown from treatment of patients with agammaglobulinemia to those with *any* primary immunodeficiency with abnormal humoral immunity [2]. Primary immunodeficiencies for which IVIG therapy may be indicated are listed in table 2. It is notable that there have not been controlled trials of IVIG use versus placebo in treating primary immunodeficiency as it was considered unethical to withhold IVIG in these patients since those treated with IVIG had dramatically better outcomes than historical controls [2]. The studies that have been performed do indicate a reduction in infection severity and incidence with IVIG treatment. A retrospective study using historical controls in patients with X-linked agammaglobulinemia showed reduced incidence of infections requiring hospitalization while IVIG was given [8]. Patients with common variable immunodeficiency were found to have a reduction in the incidence of pneumonia when on IVIG compared to when they were not in a retrospective 'before and after' trial [9]. Compared with standard dose (400 mg/kg every 4 weeks) IVIG, a high-dose (600 mg/kg every 4 weeks in adults) regimen significantly reduced the number and duration of infections in patients with primary hypogammaglobulinemia in a multicenter, double-blind, randomized, crossover study [10].

In contrast to the well-accepted importance of IVIG therapy in primary immunodeficiency with hypogammaglobulinemia or agammaglobulinemia, the role of IVIG in IgG subclass deficiency is not as clear. There have been reports of increased infections in patients with IgG subclass deficiency [11]. There have not been any randomized, double-blind, placebo-controlled trials, but IVIG is currently recommended only if these patients have a well-documented defect in the production of antigen-specific antibodies [4].

It is noteworthy that the subcutaneous route of administration is a viable alternative route of administration for some patients on chronic immunoglobulin replacement therapy. For some patients, such a route can be more convenient because it can be self-administered, but requires weekly injections that can be time-consuming [12]. An international crossover study was performed in 40 patients that showed no differences in outcomes between the 1-year intravenous and subcutaneous treatment periods [13].

Kawasaki Syndrome

The Kawasaki syndrome is an acute vasculitic disease affecting infants and young children. It is of unknown eti-

Table 2. Primary immunodeficiency diseases for which IVIG may be indicated

X-linked agammaglobulinemia
X-linked immunodeficiency with hyper-IgM syndrome
Autosomal recessive agammaglobulinemia
Autosomal recessive hyper-IgM syndrome
IgG subclass deficiency with specific antibody deficiency
Severe combined immunodeficiency
Common variable immunodeficiency
Wiskott-Aldrich syndrome
Ataxia-telangiectasia with specific antibody deficiency

ology. Early treatment with IVIG along with aspirin has been proven in multiple randomized controlled trials (RCTs) and meta-analyses [14–16] to significantly reduce the incidence of coronary artery aneurysms, the main complication that results from untreated Kawasaki syndrome. In addition, IVIG has also been effective to treat recurrent fever in this disease 2–3 days after initial IVIG dosing [17]. Clearly, IVIG is the treatment of choice for Kawasaki syndrome and no alternative has equal efficacy.

Allogenic Stem Cell Transplant (in Patients 20 Years Old or Older)

The allogenic bone marrow transplant (BMT) patient is at risk for infection due to immunosuppression from pre-BMT preparative agents, graft-versus-host disease (GVHD), and delayed immunocompetence during the post-engraftment period. IVIG is used in association with allogenic BMT as early prophylaxis against cytomegalovirus (CMV) infection, GVHD and as post-engraftment prevention against infection by encapsulated bacteria. This use of IVIG is a matter of controversy despite numerous trials that have studied this area. Many of the trials have had contradictory results and findings that failed to meet statistical significance [1]. In 1993, Bass et al. [18] performed a meta-analysis of 12 studies including 1,282 patients and found that IVIG or anti-CMV-hyperimmune IVIG reduced fatal CMV, CMV pneumonia, non-CMV interstitial pneumonia, and total mortality in both CMV-negative and CMV-positive patients. Despite the overall conclusion of efficacy, it is important to note that none of the studies were blinded and three were not randomized. Regarding GVHD, the meta-analysis found benefit of statistical significance in one of three studies that reported on GVHD, and even then the effect was limited to subjects older than 19. Since their analysis, a non-randomized,

open, historically controlled trial of 45 allogenic BMT recipients treated with high-dose IVIG for 3 months after BMT found no difference in symptomatic CMV infection, GVHD, or other infections and reported that the IVIG group had a higher incidence of fatal veno-occlusive disease of the liver [19]. A Finnish RCT of 28 CMV-seronegative patients that received a BMT from a seropositive donor found that anti-CMV-hyperimmune IVIG did not have a beneficial effect on GVHD, CMV infection, or mortality [20]. Another RCT found that monthly IVIG given from day 90 to 360 after transplantation did not reduce GVHD, bacteremia, or mortality and may have impaired long-term recovery of the humoral immune system [21]. Of note, IVIG has not been found to be beneficial in autologous BMT recipients [1, 22].

Based on the variable results from the studies, the usefulness of IVIG for allogenic BMT is not certain. It seems to be of greatest benefit to CMV-seronegative patients who receive only seronegative leukocyte transfusions and who have seronegative bone marrow donors [1]. The effect of IVIG in preventing acute GVHD is marginal, not seen in recent studies, and requires large amounts of IVIG. Therefore, despite the FDA approval in allogenic BMT, further controlled and blinded trials are needed to delineate the appropriate role of IVIG.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder usually of B-cell origin that is commonly treated with corticosteroids and alkylating agents. The disease often results in impaired immunity with hypogammaglobulinemia, which contributes to infectious morbidity and mortality. Corticosteroids and alkylating agents can exacerbate the immunodeficiency. IVIG therapy as prophylaxis against infection has been shown to reduce bacterial infections in several double-blinded [23, 24] and open [25, 26] RCTs. One of these studies showed that even low-dose IVIG (300 mg/g every 4 weeks) was effective at 6 and 12 months [26]. IVIG is widely used in CLL with hypogammaglobulinemia or recurrent infections, but some experts call for more studies on IVIG prophylaxis in CLL, pointing out the lack of improvement in survival and issues of cost-effectiveness with this therapy [1].

Idiopathic Thrombocytopenic Purpura

ITP is an autoimmune disorder characterized by antiplatelet antibodies that coat platelets, targeting them for phagocytosis by the reticuloendothelial system [1]. Most of these patients will have spontaneous resolution of the

disease with no therapy, and the small number that do require therapy may be treated with systemic corticosteroids, IVIG, or splenectomy. In initial treatment of childhood acute ITP, IVIG has been shown to be at least as effective as [27, 28] and faster acting [29] than corticosteroids or no treatment in RCTs.

In childhood ITP that is chronic or that has not responded to corticosteroids, the data for IVIG are more limited. A prospective, uncontrolled trial in pediatric chronic ITP patients or those that failed to respond to initial corticosteroid treatment or had become corticosteroid-dependent showed that IVIG resulted in a universal initial improvement and a long-term benefit in 62% of patients [30]. Another small randomized trial found IVIG to be superior to high-dose dexamethasone in the short-term but inferior to the steroid in inducing long-term remission [31]. The authors caution against meaningful comparisons between the treatment groups given the limited size of the study ($n = 23$). No studies have shown reduced morbidity or mortality from IVIG use in children with ITP [32]. Consensus guidelines recommend IVIG use in pediatric ITP patients as initial treatment if there is evidence of severe bleeding, if there is a very low platelet count with less severe bleeding or minor purpura, but not in those who have only minor purpura or are asymptomatic if platelets are $>30,000/\text{mm}^3$ [32].

Treatment of adult ITP is not as well studied. One small prospective but uncontrolled trial found no difference in efficacy between initial treatment with prednisone or IVIG in adult ITP patients [33]. One randomized but uncontrolled trial found that in adults with severe acute ITP, initial treatment with IVIG followed by prednisone was more effective than high-dose dexamethasone followed by prednisone, although the steroid-only regimen was also effective [34]. Other uncontrolled trials in adults with chronic ITP refractory to steroids and/or splenectomy have shown that IVIG can be effective but sometimes may require repeated courses to maintain a stable platelet count [35, 36]. Since no trials have compared IVIG to placebo in adults, recommendations for its use are based on the above uncontrolled trials and opinion. Generally, consensus opinion suggests IVIG as initial treatment only in adults with severe life-threatening bleeding with platelets $<50,000/\text{mm}^3$ [32]. IVIG was deemed inappropriate in patients if they had platelets between 30,000 and 100,000/ mm^3 and were asymptomatic or had only minor purpura [32]. There is no consensus opinion for adult ITP patients who have lower platelet counts and are asymptomatic/have only minor purpura or for those with risk factors for bleeding [32].

Therefore, although IVIG use as initial therapy is based on rigorous evidence in acute ITP in children that have very low platelet counts or severe bleeding, evidence for use in chronic pediatric ITP and in adult ITP is based largely on uncontrolled studies and expert opinion.

Pediatric HIV Infection

Pediatric patients with HIV infection, unlike their adult counterparts, often have early and significant humoral immunodeficiency, which can manifest as high levels of nonspecific antibodies reflecting polyclonal B-cell activation, but decreased specific antibody formation, with resultant problems with bacterial infections. Several large, placebo-controlled RCTs in children with HIV have shown that prophylaxis with IVIG can decrease the incidence of infections (including pneumonias) and hospital admissions. One trial occurred before azidovudine was commonly used, limiting the applicability of the study today [37]. Another trial only showed benefit in patients not on prophylactic trimethoprim-sulfamethoxazole, putting the effect of IVIG in question again in patients treated by current standards of prophylaxis [38]. Another concern is that neither of these trials improved mortality figures. Additional studies in the setting of today's highly active antiretroviral treatment have not been conducted, further limiting the evidence for this indication. In practice, many clinicians will use IVIG in pediatric HIV patients only if they have hypogammaglobulinemia or if they suffer from recurrent or severe encapsulated bacterial infections even after prophylaxis with trimethoprim-sulfamethoxazole [2].

Indications with Substantial Evidence for Use as a First-Line Option

Guillain-Barré Syndrome

The Guillain-Barré syndrome (GBS) is a demyelinating polyneuropathy of subacute onset that is likely due to autoantibodies against bacterial antigens that, via molecular mimicry, recognize glycolipids and gangliosides in neural tissues [39]. A large controlled trial showed that IVIG used in acute GBS resulted in improved muscle strength in significantly more patients than did plasma exchange (PE) therapy [40]. IVIG in this trial was associated with fewer adverse effects and need for artificial ventilation. The addition of IVIG to PE has not been shown to be better than either therapy alone [41], and a recent systematic review concluded that there was no evidence of superiority of IVIG over PE [42]. However, given the sometimes

limited availability of PE and the high prevalence of contraindications to PE, IVIG is considered to be the treatment of choice for GBS [39, 43].

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP), a progressive disease with data supportive of pathogenesis related to molecular mimicry, antiglycolipid antibodies, and pathologic T-cell function, presents with weakness, sensory loss, and loss of reflexes [39]. IVIG in this disease has been shown to be a useful first-line therapy in a randomized, placebo-controlled trial [44]. Rigorous trials have also shown that IVIG has similar efficacy to PE [45] and possibly slightly better efficacy than steroids [46], which have been considered the gold standard treatment for CIDP. Combination therapy has not been proven to be of increased efficacy [39]. Although there is concern that the cost-benefit ratio relative to steroids may be high with IVIG for CIDP, this ratio is likely to be lower once long-term side effects of corticosteroids are considered [47]. This is of particular importance in CIDP since it tends to be a more chronic, progressive or relapsing disease that may require prolonged treatment regimens [39].

Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a disease marked by a slow progression of motor weakness, often distal and involving the forearms [39]. Steroids are not effective in treating MMN and can exacerbate the disease, but IVIG has been shown in various RCTs to be effective in improving disability and muscle strength in the short term [48–50]. Significant improvement was found even in patients treated again after recurrence of symptoms following initially successful treatment with IVIG [51]. Although IVIG seems to be the treatment of choice for MMN and it has long-term benefit, a RCT has shown that the disease does continue to progress despite maintenance IVIG [52].

Dermatomyositis

Dermatomyositis (DM) is an inflammatory myopathy associated with rash. Microangiopathy associated with muscle fiber necrosis is associated with complement activation and deposition of membrane attack complexes on the vessel walls [1]. A single double-blind, placebo-controlled trial of patients with treatment-resistant DM found IVIG to be markedly superior to placebo in improvement of muscle strength, neuromuscular symptoms, rash, as well as histopathologic and immunopathologic parame-

ters [39]. Based on this information, IVIG is considered by some to be an important option for DM resistant to standard therapies such as steroids or conventional immunosuppressants [39]. Others feel that IVIG is a valid first-line therapy and should be used as a steroid-sparing agent [1].

IgM Paraproteinemic Demyelinating Neuropathy

IgM paraproteinemic demyelinating neuropathy is another autoimmune neuropathy due to anti-myelin-associated glycoprotein IgM antibodies that deposit on myelin and cause demyelination [39]. Two RCTs exist in this area. The first small trial showed a modest improvement in strength in only 18% of patients [53]. The more recent trial was slightly larger and showed a significant decrease in overall disability with IVIG on secondary outcomes. A long-term follow-up was not conducted. Given that other therapies such as steroids and PE have been shown to be of benefit in IgM paraproteinemic demyelinating neuropathy by only open trials, some experts recommend that IVIG may be considered in this neuropathy but should not be continued if acute benefit is not seen [54].

Stiff-Person Syndrome

The stiff-person syndrome is an autoimmune central nervous system disorder in which patients have high titers of antibodies against glutamic acid decarboxylase 65 and experience symptoms of stiffness and spasm of muscles [39]. One small RCT found that IVIG produced substantial improvement in symptoms and decreased anti-glutamic acid decarboxylase 65 levels [55]. Especially since there is not another adequate treatment for the stiff-person syndrome, IVIG can be considered for first-line treatment.

Desensitization of HLA-Allosensitized Patients Awaiting Renal Allograft Transplant

Organ transplants are often delayed or never occur due to high-level sensitization to potential donor HLA [56]. High levels of preformed anti-HLA antibodies, which are formed after exposure to nonself HLA antigens during procedures such as prior blood transfusions, organ transplants, or pregnancies, have traditionally been a contraindication to transplant. Given the already small supply of donor organs, a patient that is highly allosensitized will face much longer waiting times before finding a compatible organ or may never find one. These patients also generally have poorer graft survival even if a donor is found [56]. Various case reports have documented the ability to use IVIG to decrease allosensitization and allow success-

ful transplant of histo-incompatible organs [57, 58]. In a randomized, double-blind, placebo-controlled trial, Jordan et al. [56] treated 101 highly allosensitized adult patients with end-stage renal disease with either IVIG or placebo before transplant. The IVIG group had lower levels of anti-HLA antibodies, higher rates of transplantation, and comparable rates of graft survival compared to placebo patients. This study provides compelling evidence for the use of IVIG pretreatment in highly allosensitized patients with end-stage renal disease awaiting renal transplant in order to increase the rate of transplantation.

Fetal/Neonatal Alloimmune Hemolysis

Both rhesus factor and AB0 incompatibilities between maternal and fetal or neonatal cells can result in autoimmune hemolysis in the fetus (erythroblastosis fetalis) or hemolytic disease of the newborn. A systematic review of four RCT trials comparing neonatal IVIG plus phototherapy to phototherapy alone for 226 newborns with proven alloimmune hemolytic disease due to AB0 or Rh incompatibility found that fewer infants in the IVIG group required PE [59]. The IVIG group infants also required decreased duration of phototherapy and had shorter hospital stays than the control group. Another RCT compared treatment with IVIG or placebo in newborns with AB0 hemolytic disease and found that the IVIG-treated newborns had reduced need for PE [60].

For pregnant women with erythrocyte alloimmunization, IVIG has been given antenatally to prevent severe fetal hemolysis. Although case reports, case series, an uncontrolled prospective trial, and a retrospective trial appear to reveal benefits from IVIG, prospective controlled trials are needed before this therapy can be recommended routinely [61, 62].

Indications with Evidence for Use as Second-Line or Later Therapy or Only in a Specific Subgroup of Patients

Myasthenia Gravis

Myasthenia gravis is an autoimmune neuromuscular disease due to autoantibodies against antigens at the neuromuscular junction. It is characterized by weakness that worsens with exercise and may be treated with anticholinesterase drugs, steroids, PE, and immunosuppressants. Two controlled trials that compared IVIG to PE found no difference in efficacy between the therapies, except that the more recent trial found that PE worked faster than IVIG [63, 64]. Given the lack of sufficient evidence of ef-

ficacy, some experts recommend that IVIG should be reserved for myasthenic crises that are unresponsive to other agents or instead of PE [39].

Lambert-Eaton Myasthenic Syndrome

Another autoimmune disorder of the neuromuscular junction is the Lambert-Eaton myasthenic syndrome, most commonly seen as a paraneoplastic syndrome. Proximal muscle weakness, ocular symptoms, bulbar symptoms, and autonomic dysfunction characterize this disease that often responds to steroids or other immunosuppressants [39]. The single RCT in this area revealed superiority over placebo in strength measures and in the reduction of autoantibodies with IVIG, but the effect was short-lived [65]. Therefore, IVIG is only recommended as an adjuvant therapy for the Lambert-Eaton myasthenic syndrome.

Inclusion Body Myositis

IVIG use in inclusion body myositis, another inflammatory myopathy, has been examined in controlled trials and produced statistically insignificant or modest improvement in strength measures over placebo, even if prednisone was also used [66–68]. However, one trial did report significantly improved duration of swallowing function, suggesting that it may be useful to consider a short trial of IVIG in patients with inclusion body myositis and severe dysphagia [66].

IVIG is sometimes effective in a variety of other conditions as a second-line or alternative treatment when traditional agents fail. In these disorders, uncontrolled studies or small series have shown that IVIG may be beneficial. Some of these indications are listed in table 3. Larger RCTs would help to confirm benefit in these conditions.

Indications with Evidence for First- or Second-Line Use but Where the Exact Role Remains Controversial

Multiple Sclerosis

Multiple sclerosis (MS), another central nervous system autoimmune disorder that may have a relapsing-remitting or chronic progressive course, has been treated with IVIG. Several controlled trials have demonstrated clinical benefit and MRI improvement using IVIG in relapsing-remitting MS (RRMS) [69–72], while no benefit was reported in controlled trials of chronic optic neuritis [73], secondary progressive MS [74], or established weakness in MS [73]. Adding IVIG to methylprednisolone for

Table 3. Other conditions for which IVIG may be considered as a second-line or alternative treatment [1, 95–97]

Hematologic	Autoimmune hemolytic anemia
	Immune-mediated neutropenia
	Parvovirus B19 infection-related chronic pure red cell aplasia (though remains standard of care)
	Neonatal alloimmune hemolysis
Rheumatologic	Systemic lupus erythematosus
	Rheumatoid arthritis
	Juvenile rheumatoid arthritis
Dermatologic	Bullous pemphigoid
	Pemphigus vulgaris
	Pemphigus foliaceus
	Epidermolysis bullosa acquisita
Inflammatory	Acute myocarditis
	Polymyositis
	Adult-onset Still's disease
	Vasculitis
	Grave's ophthalmopathy

treatment of acute attacks of MS was not found to be of added benefit in an RCT [75]. Authors of a recent meta-analysis of IVIG in RRMS recommend that IVIG be considered an alternative second-line therapy when patients are intolerant of approved primary treatments. They acknowledge that the studies are concordant in terms of benefit noted in each study, but they note that differences in study design, endpoints, dosing of IVIG, and lack of some expected regression to the mean in placebo groups keeps them from recommending this treatment as a first-line option [76]. However, authors of a 2004 RCT [69] showed that IVIG after the first demyelinating attack suggestive of MS led to a delay in the second attack and MRI progression. These authors suggest that IVIG is useful as first-line therapeutic option. This highlights the controversy on the exact role of IVIG in RRMS.

Indications with Evidence of Dramatic Improvement in Uncontrolled Trials, Lack of Evidence from Controlled Trials, but Where IVIG Has Become the Standard of Care

Parvovirus B19 Infection

Human parvovirus B19 is a DNA virus that infects red blood cell precursors, causing mild self-limited disease in immunocompetent hosts, but which can cause severe and

persistent anemia in patients with underlying chronic hemolysis (e.g. sickle cell anemia) or in those who are immunosuppressed (e.g. status after organ transplant or AIDS) [4]. There are no controlled clinical trials done in this field. However, case reports [77, 78] and small case series [79–81] have often shown dramatic improvement in anemia and symptom resolution, even on retreatment for recurrences. Since no other specific therapy (e.g. antiviral) is available, and since immunosuppression may be prolonged in some of these patients, IVIG has become the standard of care for parvovirus B19-related persistent anemia in immunosuppressed patients [4]. Controlled trials in the future are needed to confirm the efficacy of IVIG in these cases.

Fetomaternal/Neonatal Alloimmune Thrombocytopenia

Fetomaternal/neonatal alloimmune thrombocytopenia occurs when maternal antibodies are produced that recognize a platelet alloantigen that the fetus or neonate has inherited from the father [82]. This disease can lead to fetal or neonatal intracranial hemorrhage (ICH), disability, or death during the first pregnancy and a very high likelihood of more severe thrombocytopenia during subsequent pregnancies [4]. For treatment, steroids can be given to the mother, but this does not prevent antenatal ICH. Alternatively, compatible platelets can be transfused into the fetus via the intrauterine route, but this process involves significant risk to the fetus. Case series have reported promising improvements in fetal platelet counts and lack of ICH in almost all IVIG-treated mothers [83, 84]. Specifically, in the 73 total mothers treated with IVIG by Bussel, no cases of fetal ICH were reported compared to 16 historical cases in untreated prior pregnancies. In the only RCT in this arena, Bussel et al. [86] compared maternal IVIG plus steroid for this disease to maternal IVIG alone with no additional benefit found by adding the steroid. Although some consider transfusion of washed maternal platelets to the fetus the treatment of choice [87], others have stated that IVIG [88] treatment of the mother is the standard of care. Systematic reviews of care for these patients highlight the lack of controlled trials from which to make an evidence-based choice among possible treatments of fetomaternal/neonatal alloimmune thrombocytopenia [82].

Other Indications

IVIG therapy has been reported as having some efficacy in numerous other diseases that are immune mediated, autoimmune, inflammatory, or idiopathic in nature but for which there are only uncontrolled trials, conflicting trial results, or a few controlled trials that have not reported benefit. Therefore, IVIG use is not recommended in these conditions outside of a controlled clinical trial. Table 4 lists these disorders for which IVIG use should be considered of questionable benefit until further supportive evidence emerges.

Risks of IVIG

IVIG is generally well tolerated, but its use clearly carries some risk. Manufacturers report adverse effects of 1–15%, but usually <5% [89]. Patients' reactions tend to be transient and mild. Common reactions may include fever, headache, myalgia, chills, nausea, vomiting, lightheadedness, back or leg pain, rash, flushing, pruritus, hypotension, hypertension, and fluid overload [2]. Often, interrupting the infusion and restarting at a lower infusion rate can abort these reactions. Less commonly, patients may have chest tightness, chest pain, wheezing, aseptic meningitis, severe headaches, or renal failure. Most episodes of acute renal failure have been associated with high-osmolality IVIG preparations with stabilizers such as sucrose. Those who experienced this side effect tended to have risk factors for renal insufficiency such as old age, hypertension, and hyperlipidemia. Aseptic meningitis seems to be more common in patients with a history of migraine. Severe hypersensitivity reactions are rare with IVIG, but may include anaphylaxis. Patients who have selective IgA deficiency rarely may have anti-IgA IgE antibodies that cause anaphylaxis during the infusion, or patients may have IgG anti-IgA antibodies that result in immune complex formation and complement activation. Interestingly however, the mere presence of IgG anti-IgA antibodies does not correlate with adverse reactions to IVIG [90–92]. Several studies have described patients with high titers of anti-IgA antibodies who are asymptomatic during infusions. Clearly, more work is needed to define the mechanism of action of anaphylactoid reactions. Other severe reactions have included thromboembolism, acute encephalopathy, bleeding disorder, stroke, neutropenia, hyponatremia, cryoglobulinemia, noninfectious hepatitis, and pleural effusion. There have been no cases of hepatitis B, HIV, or prion disease transmission due to IVIG, but

Table 4. Disorders in which IVIG is not recommended at this time [1, 39, 95, 97, 98]

Neurologic	Intractable childhood epilepsy Rasmussen encephalitis Alzheimer's disease Central pontine myelinolysis	Amyotrophic lateral sclerosis Isaac's syndrome Autism Recurrent acute disseminated encephalomyelitis
Infectious	Sepsis Pediatric head trauma ^a Solid organ transplantation ^a Refractory <i>Clostridium difficile</i> colitis	Recurrent otitis media Severe burn patients ^a Preterm infants ^a
Rheumatologic	Primary Sjögren's syndrome	Behçet's syndrome
Hematologic	Neutropenia after BMT Thrombotic thrombocytopenic purpura Acquired factor VIII inhibitors Acute lymphoblastic leukemia Hemolytic transfusion reaction	Heparin-induced thrombocytopenia Acquired von Willebrand's disease Maternal IVIG for fetal-alloimmune hemolysis Nonimmune thrombocytopenia Hemophagocytic syndrome
Dermatologic	Delayed-pressure urticaria Atopic dermatitis Toxic epidermal necrolysis/Stevens-Johnson syndrome	Autoimmune idiopathic urticaria Psoriasis
Inflammatory	Asthma	Inflammatory bowel disease
Miscellaneous	Recurrent miscarriage Drug-induced hypersensitivity syndrome Congestive heart failure Chronic sinusitis Antibody-mediated renal allograft rejection Diabetes mellitus Membranous nephropathy Acute renal failure	Pregnancy in antiphospholipid syndrome Cystic fibrosis Recurrent in vitro fertilization failure Amyloidosis Chronic fatigue syndrome Congenital heart block Nephrotic syndrome Uveitis

^a Prophylaxis against infection.

there were outbreaks of hepatitis C felt due to IVIG contamination and inadequate viral inactivation in several products during the late 1990s [93]. Since then, additional viral inactivation measures are in place, but the risk can never be eliminated fully.

Mechanisms of Action

We have yet to fully understand all of the mechanisms by which IVIG may be exerting its effects. Nevertheless, in vitro and in vivo evidence, evidence gathered from the effect of IVIG on autoimmune diseases, as well as hypotheses based on other knowledge of immune function produce a picture of some mechanisms probably at work when IVIG is administered [94]. Antigen-specific IgG found in IVIG may play a role in providing 'replacement' antibody function in primary immunodeficiencies [1].

IVIG supplies anti-idiotypic antibodies that can neutralize pathologic IgG (autoantibodies) and modify the response of B cells, modulating the immune response [94]. The Fab portion of IgG in IVIG is able to bind cytokines and lymphocyte receptors. This interaction can inhibit inflammatory cell activation, expansion, function, and viability [7]. Bacterial superantigens are also a target for IgG Fab in IVIG, and provide another mechanism for the prevention of inflammation [7]. IgG Fab binding of complement reduces complement deposition in tissues. In this fashion, tissue damage may be prevented in autoimmune disorders. The Fc portion of IgG in IVIG can block Fc-γRIII, preventing attack by phagocytes [94]. Aggregates of IgG in IVIG can stimulate production of anti-inflammatory cytokines, while monomeric IgG can increase catabolism of pathologic autoantibodies [94]. Some effects of IVIG are felt not to be IgG mediated. Soluble factors like HLA, TGF-β, CD4, and CD8 molecules that may be

Table 5. Proposed mechanisms of action for IVIG [1, 7]

1	Anti-idiotypic binding (neutralization of pathologic IgG, modifies B-cell activity)
2	Anti-cytokine and anti-B- and T-cell receptor binding via Fab to inhibit cell activation, expansion, function, and viability
3	Anti-complement binding via Fab to reduce deposition of complement onto tissues and complement-mediated tissue damage
4	Neutralization of superantigens via Fab
5	Blockade of Fc γ receptors (with inhibition of phagocytosis)
6	Inhibition/activation of complement via Fc interactions
7	Stimulation of production of anti-inflammatory cytokines
8	Increased catabolism of pathologic autoantibodies
9	Effects of soluble HLA, CD4, CD8 molecules that may be present as 'contaminants' in IVIG
10	Antigen-specific IgG replacement in immunodeficiencies

present as 'contaminants' in IVIG can inhibit cell activation and viability [7]. These varied processes may be occurring independently or in a combined fashion to produce modified inflammatory responses and immune function [7]. These mechanisms are summarized in table 5.

Recommendations for Appropriate Use of IVIG

As is clear from the numerous conditions discussed above, IVIG is being used for a wide array of disorders. Based on the presence or absence of controlled clinical trials or other compelling evidence we can define more restricted groups of indications for the appropriate use of IVIG.

There is no doubt that IVIG is indicated in the treatment of primary humoral immunodeficiencies. This first indication of IVIG is in some ways an exception to the rule about controlled trials. Although such trials are lacking and will not be ethically feasible in the future, the overwhelming historical evidence suggests that IVIG is the primary treatment for humoral immunodeficiency. When considering IgG subclass deficiency, however, the lack of controlled, clinical evidence for efficacy suggests that treatment should not be considered for such patients without evidence of specific antibody production deficits and clinically significant infections. Even in those with such deficits, the lack of controlled data would make it appropriate to limit IVIG use in these patients to controlled, clinical trials. Since single institutions are unlikely to

have enough patients to design a clinical trial, there is a need for cooperative projects to be designed and implemented.

As discussed above, other indications have significant controlled, clinical trials that have shown efficacy of IVIG therapy, making its use appropriate. These indications include: Kawasaki's syndrome, CLL infectious prophylaxis, acute pediatric ITP (initial treatment if the platelet count is <30,000 or if significant bleeding has occurred), allogeneic BMT, pediatric HIV with hypogammaglobulinemia or bacterial infections despite antibiotic prophylaxis, GBS, CIDP, MMN, DM, IgM paraproteinemic demyelinating neuropathy, stiff-person syndrome, highly allosensitized patients with end-stage renal disease awaiting renal transplant, patients with inclusion body myositis and severe dysphagia, and RRMS.

Another group of indications warrants special comment. In this group, although efficacy proven by controlled, clinical trials is not yet available, uncontrolled trials or small case series have shown efficacy. Ideally, these conditions should be rigorously studied in the framework of large RCTs. However, many of these conditions often fail first-line therapy and are progressive. In such a setting, we and experts in the respective fields [1, 95–97] feel it is appropriate to consider a trial of IVIG as a second-line or adjunctive agent. These conditions are listed in table 3. Other conditions that fit in this group include myasthenia gravis, Lambert-Eaton syndrome, and fetomaternal/neonatal alloimmune thrombocytopenia (my reading of the experts is that this is a condition for which maternal IVIG is effective).

Parvovirus B19 infection is in a group of its own since it is a disease with case series showing dramatic improvement, with no alternative treatment that works, and IVIG is considered the de facto standard of care. Despite the lack of controlled trials in this disease, IVIG use is appropriate given the above factors.

The largest group of disorders unfortunately falls into our last category. For these conditions, in addition to a lack of controlled trials, the trials that exist show only conflicting results or have shown absence of benefit. Expert opinion suggests that IVIG therapy is not appropriate for these conditions, and it is recommended that these conditions, listed in table 4, should not be treated with IVIG therapy until further evidence is gathered in the setting of controlled trials. Some of the conditions that fall into this group include adult ITP and chronic pediatric ITP, secondary progressive MS, chronic MS-related optic neuritis, and established MS-related weakness.

Conclusions

IVIG is a complex therapeutic agent that, based on current data, appears to harness the actions of various parts of the human immune system to deliver its effects. Our understanding of its mechanisms of action is incomplete. This may be one reason that IVIG is used in such a wide variety of disorders. As there is expansion in our understanding of its mechanisms of action and in understanding the diseases we use it to treat, appropriate use will be likely easier to define and achieve. Although the FDA-approved list of indications is short, off-label use of IVIG is significant. This situation is likely encountered around the

globe. In fact, by some reports, off-label use exceeds approved use [5]. Cost and potential risks of treatment are two reasons why we must make every effort to limit IVIG use to those indications where the evidence is of sufficient quality and quantity. Another reason is that haphazard use for indications that are not appropriate will decrease the supply of IVIG for disorders that currently have no other form of treatment. To address these problems, it appears that within specialties, establishment of registries of IVIG use in disorders for which evidence is lacking would be a first step, particularly in rare diseases. At the least, such registries could facilitate initial case control studies and lead to RCTs.

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