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Review

Intravenous immunoglobulin (IVIG): modes of action in the clinical management of recurrent pregnancy loss (RPL) and selected autoimmune disorders

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Abstract

Recurrent pregnancy loss has been associated with autoimmune responses to membrane phospholipids and alloimmune reactions against paternally derived molecules on the trophoblast. The problem is psychologically and economically stressful as it undermines the capacity of some couples to reproduce and participate effectively in the day-to-day economic activities. This article reviews the adoption of intravenous immunoglobulin as a form of therapy for the clinical management of recurrent pregnancy loss and of selected autoimmune disorders. Side effects, contraindications and safety of use are discussed.

Keywords: autoimmune disorders; intravenous immunoglobulin; recurrent pregnancy loss.

Introduction

Pathophysiology of antiphospholipid-mediated pregnancy loss results largely from increased platelet aggregation, decreased endogenous anticoagulant activity, increased thrombosis and decreased fibrinolysis, i.e., disorders leading to uteroplacental thrombosis and vasoconstriction following immunoglobulin binding to platelets and to endothelial membrane phospholipids (1, 2).

The observation that monoclonal antibodies to phosphatidylserine inhibit intracellular fusion of human trophoblast cell lines in vitro (3, 4) and can impair both trophoblast hormone production and invasion in vitro (4) provides experimental evidence in support of antiphosphatidylserine-mediated pregnancy loss. Women with a history of recurrent pregnancy losses (loss of three or more consecutive pregnancies before 20 weeks of gestation) show a higher percentage of autoantibodies to various cell and tissue components than women with no history of reproductive failure (5). Additional reports (6) indicate that women with repeated miscarriages possess high levels of anticardiolipin antibodies (ACA) and that pregnancy success rates in women with medium to high ACA were significantly lower than those that did not have ACA (64% vs. 96%). Such observations have led to the speculation that autoimmunity to other cellular components and tissues may cause reproductive failure or that reproductive failure may be a manifestation of some undiagnosed autoimmune disorder (7). However, whether or not antiphospholipid antibodies are the cause or a consequence of reproductive failure or may be artifacts related to prior reproductive losses is unclear. This article provides background information supporting the notion that reproductive failure may result from autoimmune responses and justifies the use of intravenous immunoglobulin (IVIG) in the management of recurrent pregnancy loss (RPL) and other autoimmune disorders

The background to the adoption of IVIG as a form of therapy for reproductive failure and immune-mediated diseases

Adoption of intravenous immunoglobulin as a form of therapy for RPL was partly based on the observations that pre-transplant blood transfusion enhanced survival of renal allografts and that such sera contained non-cytotoxic Fc receptor blocking antibodies whose presence was associated with improved survival of renal allografts (8, 9).

Other reports indicated that placental immunoglobulin (Ig) G could alleviate rheumatoid arthritis (10), which is a disease of immune dysfunction. The observation that the human leukocyte antigen-G, HLA-G, expressed on placental trophoblast was truncated (11) raised the possibility that this could protect the feto-placental unit from direct attack by the maternal immune system. Other studies (12) indicated that progesterone-induced inhibitory factor (PIBF) down-reg-

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Table 1 Antibody subclass composition of IVIG.

Product	Source	% composition of IgG				Others	% purity
		IgG1	IgG2	IgG3	IgG4		
Sandoglobulin	ZLB	66	27	4.3	2.2	14.8 IU	99.5
Cytotect Biotest	Biotest	62	34	0.5	3.5	5 mg/ml IgA + anticytomegalovirus	95
Varitect CP	Biotest	59	36	3	2	2.5 mg/ml IgA	95
Varitec	Biotest	62	34	0.5	3.5	5 mg/ml, IgA Antivaricella-Zoster antibodies 25 IU	95
Polyglobin	Bayer Vital	63.2	29.6	5.7	1.3	0.16 mg IgA	98
Octagam IgG	Octapharmaceutical	68	28.6	6.4	1.1	0.1 mg IgA, 0.1 mg IgM+ 0% maltose	–
Intraglobulin	Biotest	62	34	0.5	3.5	2.75 g/100 ml glucose	95
Pentaglobulin	Biotest	3.8 g IgG				0.6 g IgM, 0.6 g IgA	–

ulated natural killer cell activity and induced synthesis of asymmetric IgG molecules. These antibodies are glycosylated on one of the two Fab arms, making them behave as univalent and not divalent antibodies, hence incapable of effector functions or the capacity to fix complement, suggesting that they may function more as antigen blockers than anti-idiotypes. That the proportion of these antibodies increased from 12.1% in non-pregnant women to 24.4% in pregnancy, and that they comprised 44.4% of IgG eluted from placenta (13), strengthened the notion that they may function as antigen blockers. The anti-idiotypic behavior of IgG further strengthened the already attractive hypotheses and provided a practical working model for IVIG. In the 1980s, IVIG was licensed for use in the treatment of primary immunodeficiency diseases characterized by hypogammaglobulinemia and/or recurrent infection (14). In such patients, administration of IVIG led to a decrease in the incidence and severity of infections. It was also found to have immunomodulatory effects and its use was subsequently extended to include selective treatment for hematological, inflammatory and infectious diseases that have an immunological component. In the late 1990s, it became abundantly clear that IVIG was to become the treatment of choice for RPL and evidently for many other autoimmune and alloimmune disorders, as well as for primary and secondary immunodeficiencies. The relative success of IVIG in the management of autoimmune disorders has led to its use in the treatment of many other diseases, including those for which placebo-controlled clinical trials have not been undertaken.

Commercial preparation of IVIG

IVIG is prepared from pooled cryopreserved human plasma from hundreds to thousands of donors by stepwise alcohol precipitation and nanofiltration. Blood for use is screened for antibodies to syphilis, hepatitis B surface antigen (HBs), hepatitis B core antigen (HBc), hepatitis C virus (HCV) and human immunodeficiency virus, HIV1 and HIV2 antigens among others. The first step in production involves precipitation with 19% ethanol pH 5.8 at -5°C followed by filtration to remove albumin. The filtrate is precipitated with 12% ethanol pH 5.1 at -3°C and subsequently with 25% ethanol pH 7.25 at -7°C. The precipitate is then filtered, freeze-dried and packaged for use. In some cases, the product is refined by chromatography while inactivation of bacteria and viruses is achieved during pre-production and production stages with a variety of methods including treatment with sulfide, β-propiolacton, polyethylene glycol, incubation with trace amounts of pepsin at pH 4.0 and nanofiltration using 20–25 nanometer filters (15). The final filtrate is stored at low temperatures to avoid degradation by proteolytic enzymes. This polyclonal preparation contains 95–99.5% IgG with variable amounts of IgA and IgM in its highly purified form and is effective in the treatment of a wide spectrum of diseases with a reasonable degree of success (Tables 1 and 3).

Possible modes of action of IVIG

IVIG is thought to achieve immunomodulation by a number of mechanisms working synergistically in different combinations to provide protection. These mechanisms include (i) induction of Fc γ-receptors IIB (FcγRIIB) on colony-stimulating factor (CSF)-independent effector macrophages, (ii) polarization of Th1/Th2 ratios, (iii) activation of neutrophils and interaction with super antigens, (iv) acceleration of autoantibody catabolism by binding to FcRn receptors on endothelial cells, (v) inhibition of IgE production by B cells, (vi) inhibition of complement activation, (vii) down-regulation of natural killer (NK) cell activity, (viii) inhibition of cytokine production, (ix) increased production of anti-idiotypic antibodies against anti-HLA antibodies or soluble HLA antigens, (x) production of anti-cytokine antibodies and (xi) down-regulation of B cell function. Different modes and combinations of these action mechanisms are observed in different disease conditions. For example, in idiopathic thrombocytopenic purpura, (ITP), where platelets are marked by antiplatelet antibodies for destruction by macrophages and other killer leukocytes, two mechanisms have been reported: (a) IVIG or its pepsin-digested Fc fragments act as competitive blockers of Fc receptors on splenic macro-

phages and other killer leukocytes and (b) by binding to idiotypic antibodies. Recent studies suggest that the more immediate effects result from the ability of Fc receptors in IVIG to induce expression of inhibitory receptors on the effector cells thereby decreasing or preventing clearance of antibody-coated platelets (16), while the anti-idiotypic antibodies may provide long-term protection (16, 17). Other studies (18) have indicated that IVIG induces expression of FcγRIIB on infiltrating macrophages and hence prevents antibody-induced inflammation. In this model, protection is achieved by a two-step mechanism in which colony-stimulating factor-1 (CFS-1)-dependent macrophages act as innate sensors for the Fc fragment of IVIG, leading to induction of FcγRIIB on CSF-independent effector macrophages and thereby raising the threshold required for FcγRIII activation and preventing autoantibody-triggered inflammation.

Given that physiological antibodies to interleukin (IL)-6 (IL-6), IL-1a, tumor necrosis factor-α, (TNF-α), IL-8 and granulocyte-monocyte colony-stimulating factor (GM-CSF) have been found in healthy individuals, it is also possible that IVIG contains natural anti-cytokine antibodies (19, 20). On this assumption, the anti-inflammatory effects of IVIG may result from neutralization of pro-inflammatory cytokines and may be responsible for the immediate relief of life-threatening conditions associated with the rapid drop of excessive serum ferritin and elevated cytokine levels observed in patients with reactive macrophage activation syndrome with no obvious microbial background (21).

IVIG has also been reported to accelerate autoantibody catabolism by binding to Fc receptor n (FcRn) on endothelial cells (22). Thus, if IgG is pinocytosed and bound in a low pH milieu to FcRn, the immunoglobulin is protected from lysosomal degradation, suggesting that IVIG may saturate FcRn receptors and through competition prevent pathogenic autoantibodies from binding, and consequently lead to accelerated degradation of pathogenic autoantibodies. This hypothesis was supported recently when IVIG led to clearance of monoclonal antiplatelet antibodies in wild-type, but not in FcRn, knockout mice (23). In another study, peripheral blood was collected from 21 recurrent aborters before, and 5 days after, the first IVIG infusion. Using a combination of monoclonal antibodies against T cell surface markers and intracellular interferon-γ (IFN-γ) and IL-4, T helper 1 and 2 (Th1 and Th2) cells were detected by flow cytometry (24). The percentage of IFN-γ producing Th1 and IL-4 producing Th2 cells and the Th1/Th2 ratios were compared between pre- and post-infusion samples. There was a significant decrease in the Th1/Th2 ratio in most of the cases. The authors concluded that administration of IVIG in such women led to the polarization of the T-helper cell population. Related studies have indicated that IFN-γ induces expression of FcγRIIB on monocytes and neutrophils, whereas IL-4 has the opposite effect (25). Accordingly, this may lead to decreased release of pro-inflammatory cytokines (26).

Given that IgG can bind the active complement factors C4b and C3b, high concentrations of soluble monomeric IgG may theoretically prevent damage of tissues by deviation of the complement cascade from target tissue to the exogenous IgG in circulation. The in vivo importance of this potential anti-inflammatory mechanism has been demonstrated in an experimental model of complement-mediated and acute inflammation (27). Also, natural anti-C3b autoantibodies have been shown to inhibit C3 convertase activity in vitro (28). According to Lutz et al. (29), anti-complement mechanisms may potentially be involved in IVIG treatment of patients with dermatomyositis.

Although several mechanisms of action have been proposed, the most commonly recognized modes of action to date appear to be those of competition for binding to the Fc receptor of phagocytic cells and the binding of anti-idiotypic antibodies to autoantibodies by attaching to the Fab portion of the idiotypic antibody molecule. Table 2 presents the proposed mechanisms of action of IVIG.

Table 2 Proposed modes of action of IVIG.

Mechanism	Reference
Induction of Fc γ-receptors (RIIB) on CSF-independent effector macrophages	Samuelsson et al. 2001 (16), Binstadt et al. 2003 (30), Bruhns et al. 2003 (18)
Polarization of Th1/Th2 ratios	Graphou et al. 2003 (24), De Placido et al. 1994 (32)
Activation of neutrophils and interaction with super antigens	Simon and Späth 2003 (31)
Acceleration of autoantibody catabolism by binding to FcRn receptors on endothelial cells	Yu and Lennon 1999 (22)
Inhibition of IgE production by B cells	Sigman et al. 1998 (33)
Inhibition of complement activation	Lutz et al. 1998 (29), Lutz et al. 1996 (28)
Inhibition of complement activation	Lutz et al. 1996 (28), Christiansen et al. 1992 (34)
Down-regulation of NK cell activity	Kwak et al. 1996 (35)
Inhibition of NK cell activity and cytokine production	Kwak et al. 1996 (35), Ruiz et al. 1996 (36)
Increased anti-idiotypic antibodies against anti-HLA antibodies or soluble HLA antigens	Maruyama et al. 1994 (37)
Presence of natural anti-cytokine antibodies	Abe et al. 1994 (19), Ross et al. 1994 (20)
Down-regulation of B cell function	Nydegger 1991 (38)

IVIG in the clinical management of RPL

IVIG is an anti-idiotype that presumably prevents cytotoxic antibody from binding non-selectively to the fetoplacental unit and down-regulates activated NK cell activity (35) and may thus convert a hostile Th1 endometrial milieu to a trophoblast-friendly Th2 environment (24, 31). It was adopted as a form of therapy for RPL following concerns that immunotherapy with leukocytes, despite high success rates (39, 40), exposed recipients to high risk of contracting other diseases, as the latter involves the use of whole cells with intact nuclear material. Thus IVIG was seen as a safer alternative to leukocyte immunotherapy (39, 41). In one study, treatment with IVIG led to increased pregnancy rates in patients undergoing in vitro fertilization and embryo transfer (IVF/ET) (42). The study included 32 women who had previously failed in more than 12 attempts of IVF/ET treatment but were efficient embryo producers with persistent elevated plasma levels of CD56+ cells. Each woman received 500 mg/kg IVIG prior to ET and if serum human chorionic gonadotropin (hCG) concentrations were positive for pregnancy, IVIG was continued at the same rate (500 mg/kg/month) until 28 weeks of gestation. The authors reported 56% and 9% pregnancy rates with and without IVIG, respectively. The live birth rate was 38% with IVIG and 0% without.

In another study, efficacy of low-dose IVIG was evaluated in women with immunological abnormalities and RPL (43). In this study, 47 women aged 28 to 45 years (mean age 37 years) with a mean of 3.7 previous abortions were enrolled. Immunological abnormalities included antiphospholipid antibodies (32%), anti-thyroid antibodies (53%), antinuclear antibodies (28%), anti-ovarian antibodies (2%), increased NK activity (40%), increased IgM levels (28%) and increased CD4/CD8 T cell ratio (15%). Thirty one of the 47 women (66%) had more than one immunological abnormality. Patients were treated with 200 mg/kg body weight IVIG within 2 weeks of attempted conception. Once conception was achieved, IVIG was continued on a monthly basis at the same dose through 26 to 30 weeks of gestation. Of the 47 women, 36 received initial treatment and 24 became pregnant. Of these, 20 continued IVIG through 26 to 30 weeks of gestation and 19 of the 20 (95%) had successful term pregnancies. Four women discontinued IVIG after 10 to 12 weeks of gestation and three of these women (75%) had successful pregnancies. No fetal abnormalities were observed in any of the successful cases. Of the 11 women who refused IVIG therapy, seven became pregnant and all seven miscarried. Elsewhere, 95 women experiencing two or more consecutive spontaneous abortions with no known cause were randomized and given either IVIG (500 mg/kg body weight/month) or placebo with albumin (44). Of these 95 women, 47 received IVIG and 48 placebo treatment. In total, 34 women were discontinued from treatment after failing to conceive within four cycles. Of the 29 women who conceived after receiving IVIG, 18 (62%) delivered live births and 11 (38%) aborted. In contrast, only 11 of the 32 women who conceived after placebo treatment (34%) delivered live births, while 21 of 32 (61%) aborted. In yet another study, it was reported that IVIG treatment used at 400 mg/kg body weight/day for 3 days every 4 weeks and anticoagulant treatment (35) led to substantial improvement in reproductive performance of recurrent aborters. The authors reported that 86.3% of women with elevated NK cells who received IVIG and anticoagulant therapy had successful pregnancy outcomes. Peripheral blood CD56+ NK cells and CD56+/CD16+ cells were significantly suppressed 7 days post IVIG infusion, while the levels of other lymphocytes remained unaffected. Also, women who delivered live born infants following IVIG treatment showed a down-regulation of peripheral blood NK cells (CD56+ and CD56+/CD16+) during early pregnancy when compared with those who miscarried the index pregnancy. In the presence of antiphospholipid antibodies, treatment with heparin and aspirin led to a significant increase in pregnancy rates among IVF patients with organic female infertility (45). However, similar treatment did not improve the outcome for patients who failed to conceive in their first treatment cycle and who underwent a second IVF cycle (46). When these patients were positive for IgG and/or IgM class antibodies against phosphatidyl serine and phosphatidyl ethanolamine, empirical addition of IVIG impacted significantly on pregnancy rates in a third IVF cycle (46, 47). While these reports show overwhelming success rates resulting from use of IVIG in RPL, a European study involving 172 women reported that the success rates with IVIG ranged from 68 to 87% (48) and that success rates due to placebo treatment were in the same range and subsequently suggested that the success rates obtained with IVIG may have been due to placebo effects. A similar observation was reported elsewhere (49). Overall, the biological significance of these data remains ill-defined because of the conflicting results reported on the efficacy of IVIG for RPLs. In the face of all these controversies, it is important that all interpretations to date be regarded as speculations requiring further investigation. However, despite the controversies surrounding the use of IVIG in the management of reproductive failure (49, 50), the positive results obtained so far are undeniably promising.

IVIG in the clinical management of other autoimmune disorders

In addition to its widespread use in the management of RPL, IVIG is currently used in the management of (i) neonatal alloimmune thrombocytopenia, (ii) idiopathic thrombocytopenia purpura, (iii) Guillain-Barre′ syndrome, (iv) chronic inflammatory demyelinating polyneuropathy, (v) systemic lupus erythematosus, (vi) Kawasaki syndrome, (vii) myasthenia gravis and Lambers-Eaton myasthenic syndrome (LEMS) (viii) rheumatoid arthritis, and (ix) in prevention of graft vs. host disease in renal allografts and bone marrow transplantations, as well as in several other autoimmune and alloimmune disorders

Neonatal alloimmune thrombocytopenia and hemolytic disease of the newborn In neonatal alloimmune thrombocytopenia (NAIT), the mother develops antibodies to fetal platelet antigens, most commonly the human platelet antigen 1a. Infants with this condition are born with clinical indications of moderate to severe thrombocytopenia and may be at risk of intracranial hemorrhage (51). As with other fetal-maternal alloimmune conditions, the risk to the fetus and the severity of the condition may be higher with each subsequent pregnancy. On administration, part of IVIG is thought to cross the placenta and provide protection to the fetus by preventing transport of maternal antibodies across the placenta and inhibiting maternal immunoglobulin synthesis through a feedback mechanism, thereby limiting platelet destruction in the fetus. Previous studies have indicated that IVIG decreased platelet destruction in 50 to 80% of the cases (51, 52) and a study carried out by Gaddipati et al. (53) linked initial fetal platelet counts to the subsequent efficacy of IVIG therapy. Thus, if the fetal platelet counts were greater than 20 000 per microliter, then approximately 89% of future counts were above that level. However, if the counts were less than 20 000 per microliter, then only 51% had an increased count after IVIG administration. Hemolytic disease of the newborn child results from production of anti-D antibodies but has been managed by use of Rh immunoglobulin (RHIg). However, some RhIg failures have been reported, suggesting that this disease may in some cases result from antibodies that target other blood group antigens. In such cases, IVIG has been shown to decrease maternal antiplatelet antibody titer. However, in cases where the maternal antibody is extremely high, as in ITP occurring during pregnancy so that intrauterine transfusion cannot be performed (51, 54), IVIG has been shown to minimize platelet damage in the fetus.

Idiopathic thrombocytopenic purpura Idiopathic thrombocytopenic purpura, ITP, is a hematological autoimmune disease characterized by destruction of antibody-marked platelets by macrophages and other killer leukocytes and can lead to bleeding disorders. It occurs in both acute and chronic forms in children and adults. Spontaneous remission occurs in 80% of untreated children but only 10–20% of adults (55). In all forms, corticosteroids and splenectomy are regarded as treatments of first choice. However, IVIG used at 400 m/kg daily for 5 days may serve as an alternative to standard treatments or where adverse effects or the need for a rapid effect in severely affected patients preclude their use. In acute ITP, management with corticosteroids has been found to be as effective as IVIG in both children (56) and adults (57). However, in chronic ITP of more than 6 months duration, IVIG should be reserved for treating episodes of active bleeding in such patients or in situations where corticosteroids alone are ineffective or contraindicated (58). The role of IVIG treatment before scheduled splenectomy, although effective in raising platelets levels rapidly, is uncertain because of the complications following the procedure, even in patients with extremely low platelet counts (56). Other reports (59) have indicated that infusion of large amounts of IVIG or polyclonal anti-D antobodies can reverse thrombocytopenia in patients with idiopathic thrombocytopenic purpura within hours of administration and that the effect of IVIG apparently outlasts several half-lives (the half-life varies for different products in different disease conditions but ranges from 24 to 40 days).

Guillain-Barre′ syndrome Guillain-Barre′ syndrome (GBS) is a neuroimmunological disease characterized by local inflammation and demyelination of peripheral nerves. It is associated with development of acute motor weakness, usually beginning in the feet and progressing to muscles of the arm and trunk. Severe forms can lead to respiratory failure, requiring admission to intensive care units (58). Although plasma exchange has been shown to reduce the rate and extent of relapse and has been regarded as treatment of choice, some studies have suggested that IVIG may be as effective (60, 61). In one study, IVIG was successfully used as a replacement treatment for patients who could not undergo plasma exchange (62). However, some reports (63) have indicated disease progression or a high relapse rate in patients given IVIG. According to Bleck (64), differences in the composition of the available brands of IVIG (Table 1) may partly be responsible for these discrepancies although this has yet to be established.

Although treatment with IVIG and aspirin was for some time considered the treatment of choice, a survey carried out in the United Kingdom (65) established that over 50% of children diagnosed in the UK did not receive optimum treatment or received it too late to be effective. In a study carried out elsewhere, the use of IVIG was associated with increased blood viscosity (66). Also, 23 children with severe GBS and who had become bedridden due to a motor disability grading scale (MDGS) of at least four were analyzed (67). Fifteen children were treated with IVIG and eight comprised the untreated group, five on supportive therapy and three treated previously with oral steroids found inefficient in GBS. IVIG was administered at a dose of 1000 mg/kg daily for 2 days under constant monitoring with no adverse effects requiring cessation of therapy. Improvement by one grade on the MDGS after IVIG therapy was achieved after a mean of 10.17 days (median 8 days), and patients started walking independently after a mean of 30.35 days (median 20.5 days). Improvement by one grade on the MDGS was achieved in the untreated group after a mean of 22.3 days (median 20.3 days), and they started to walk independently after a mean of 113.3 days (median 100 days). The authors recommended the use of IVIG as the first line drug in such cases. According to Azulay et al. (68), IVIG and plasma exchange are the gold standard therapies for the demyelinating form and probably for the other variant of GBS despite the absence of controlled trials.

Chronic inflammatory demyelinating polyneuropathy Chronic inflammatory demyelinating polyneuropathy is a chronic form of GBS in which both steroids and plasma exchange have been shown to be effective. IVIG and plasma exchange were equally effective in a controlled comparison but the benefits of both treatments were found to be short-lived (58). Treatment costs were estimated to be similar for both groups, although there was considerable variation in the dosing schedules found to be effective (69). The optimum number of infusions and frequency of treatment courses remain to be determined. Accordingly, it was suggested (58) that IVIG should be reserved for patients with progressive disease who are severely disabled and in whom other treatments have failed.

Systemic lupus erythematosus Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease with diverse clinical manifestations ranging from mild clinical features to a life threatening condition. Potential life threatening organ involvement may remain asymptomatic until irreversible damage has occurred and associated fatigue, though not life threatening, can be quite debilitating (70). Although the actual cause of the disease is not known, it is thought to arise from a combination of genetic, environmental and hormonal factors with major dysfunction of the immune system due to autoantibodies (70). Abnormalities include high titers of autoantibodies to a vast array of tissue antigens with the most characteristic being those directed against components of the cell nucleus such as DNA, RNA, histones, nuclear proteins and protein-nucleic acid complexes. The clinical course of SLE is highly variable and unpredictable, frequently involving periods of remission and relapses (71). Current therapies include a broad spectrum of steroids and immunosuppressive cytotoxic drugs and the methods being investigated include manipulation of secondary stimulation of immune responses (anti-CD40L9), manipulation of cytokines (monoclonal anti-IL-10), inducing tolerance by administration of blocking peptides (LJP394) and manipulation of idiotypes by IVIG (72). Pharmacological management involves four main classes of drugs often given in combination. These include non-steroidal anti-inflammatory drugs, anti-malarials, corticosteroids, and cytotoxic drugs (70). The cytotoxic drugs in use include azathioprine or cyclophosphamide together with corticosteroids often in high doses. Available evidence suggests that a combination of pulsed methylprednisolone and cyclophosphamide is superior to cyclophosphamide alone (73, 74). Although corticosteroids and cytotoxic drugs have improved the survival of SLE patients remarkably over the past decades, such medications have powerful anti-inflammatory and immunomodulatory effects and their use is severely limited by immunosuppression, myelosuppression and/or numerous other frequent side effects. A safe and efficient mode of immunomodulatory therapy for this disorder is therefore still lacking. It is on this premise that high-dose IVIG has been used in patients with severe thrombocytopenia, since IVIG is immunoregulatory but not immunosuppressive or myelotoxic. However, in addition to being capable of modulating SLE, IVIG may also provide a defense against infection rather than encourage it. In one study, Ait Benhaddou et al. (75) reported two cases of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a rare form of SLE complicated by respiratory failure. In the first case, pure motor AIDP was the first manifestation of SLE and the patient responded well to prednisone treatment with dramatically good regression of clinical deficit and normalization of nerve conduction within 1 month and 12 months of treatment, respectively. In the second case, AIDP occurred only 1 week after diagnosis of SLE and corticosteroid therapy. Clinical improvement was obtained after two doses of IVIG and normalization of nerve conduction was obtained within 8 months. It has also been suggested that addition of IVIG or plasmapheresis (PP) may be necessary although corticosteroid therapy may be sufficient (75) in some cases.

IVIG has also been used successfully in the treatment of neonatal lupus erythematosus in six cases at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand. The victims presented with cutaneous lesions, thrombocytopenia, hepatosplenomegaly and mild elevation of liver enzymes (76). Skin rashes erupted at 3 to 6 weeks of age. With the exception of thrombocytopenia all the abnormalities resolved spontaneously upon administration of IVIG. Three of six patients needed blood transfusion to replace gastrointestinal bleeding. IVIG used at 2000 mg/kg body weight was given in three cases with good response in two of the three cases. Platelets rose rapidly and maintained at normal level within 24 to 48 hours. Combined therapy with corticosteroids of 2 mg/kg body weight was given in one case with good outcome. The authors concluded that IVIG at a dose of 1000 mg/kg body weight for 1 to 2 days is an effective treatment for SLE with severe thrombocytopenia, especially when a corticosteroid is contraindicated.

According to some reports (77, 78), using IVIG in the treatment of SLE is at present limited by cost, poor understanding of the mechanisms of action and conflicting results presented in the literature regarding clinical efficacy.

Kawasaki syndrome Kawasaki syndrome is a self-limiting disease that leads to coronary artery lesions (79) and is a leading cause of acquired heart disease in North America and Japan. It is a systemic vasculitis with cardiac and non-cardiac complications whose cause is unknown, although infectious agents have been suggested and anti-endothelial cell antibodies are usually found in many patients. The disease commonly occurs in children under 5 years of age and can lead to significant morbidity and mortality. There is evidence to suggest that IVIG may relieve the condition by decreasing circulating cytokines that mediate much of the damage. In one study (80), treatment with IVIG in combination with aspirin reduced the incidence of coronary abnormalities from 18% to 4% at 7 weeks after administration. Such treatments during the first 10 days of the syndrome are now considered

the treatment of choice and according to Newburger et al. (81), a single dose of IVIG 2000 mg/kg given over 10 hours is as effective and as safe as 400 mg/kg/day given over 4 days and is advocated by some medical doctors as standard therapy (82). However, the risk of adverse reactions, in particular aseptic meningitis, may be higher with the single-dose regimen. In a study carried out elsewhere (66), it was indicated that high-dose IVIG reduces the risk of coronary artery aneurysms for Kawasaki patients. Although IVIG therapy in such cases may increase blood viscosity in vitro and in vivo and can theoretically lead to cardiovascular or cerebrovascular thromboembolism in adults (66), the authors concluded that the use of IVIG therapy for Kawasaki disease might be relatively safe with no risk of thromboembolism due to hyperviscosity. Also, a survey carried out in the United Kingdom (65) established that over 50% of children diagnosed in the UK did not receive optimum treatment or received it too late to be effective (58).

Myasthenia gravis/Lambert-Eaton myasthenic syndrome Myasthenia gravis is an autoimmune disorder of neuromuscular transmission characterized by weakness of voluntary muscles. It is caused by autoantibodies to acetylcholine receptors and hence interferes with nerve impulse transmission and affects both men and women of any age. Several small studies have shown IVIG to be effective and 70% of patients responded with improvement of at least one grade in the severity of their disease in a larger open study (58). However, in most patients the response was short-lived and sustained only by a repeated course of therapy (83). According to Stricker et al. (84), IVIG may not act as rapidly and reliably as plasma exchange in myasthenia gravis and they suggested that its use should be limited to critically ill patients where alternative immunosuppresive measures are unavailable or contraindicated. Lambert-Eaton syndrome is a related autoimmune condition, with symptoms similar to those of myasthenia gravis. A randomized, double-blind, placebo-controlled crossover trial in nine patients indicated that IVIG improves muscle strength and leads to a decrease in antibody levels (85). However, whether or not IVIG may eventually become established as an adjunct to conventional therapy is a subject of further investigation.

Rheumatoid arthritis Rheumatoid arthritis (RA) results from a combination of several predisposing factors including relations between epitopes of trigger agents, usually viruses, self antigens and histocompatibility epitopes, namely human leukocyte antigen. Normal serum estrogen and low androgen levels, but high synovial fluid estrogens and much lower androgen levels, have been found in RA patients supporting a fundamental role of peripheral sex hormone metabolism in the manifestation of the disease (86).

Symptoms may include cutaneous ulcerations, mononeuritis and visceral damage based on systemic vasculitis (87), painful swollen joints, purpura, muscle weakness and bilateral scleritis. In one report, a 50-year-old female patient with malignant RA was subjected to 1000 mg methylprednisolone every 24 hours for 3 days followed by 60 mg oral prednisolone daily and 800 mg of intravenous cyclophosphamide but she gradually deteriorated (88). On day 14 of hospitalization, the patient underwent an operation because of perforations of an ileum ulcer proven to be caused by vasculitis. Although the operation and recovery were successful and infection was excluded by extensive examinations, high fever and inflammatory findings continued. The effect of PP and immunosuppressive treatment was transient. However, IVIG used at a dose of 400 mg/kg body weight/day for 5 days 60 days after the operation was successful. Immunosuppressive drugs were maintained at the same dose during IVIG treatment and clinical improvements were seen 3 days after initiation of IVIG. This was followed by improvements in laboratory variables including C-reactive protein and C-anti-neutrophil cytoplasmic antibodies both finally becoming normal. The patient went into remission without adverse effects after 1 month. Table 3 shows this efficacy of IVIG in the treatment of RPL and other autoimmune diseases.

Renal allografts and bone marrow transplantation Studies by Rocha et al. (96) associated enhanced graft loss with acute humoral rejection (AHR). The study compared renal allograft survival of patients with AHR treated with PP and IVIG with allograft survival in patients with acute cellular rejection (ACR). The authors retrospectively analyzed all kidney transplants performed at the Department of Medicine, Duke University Medical Center, Durham, North Carolina between January 1999 and August 2001 ($n=286$). Recipients were classified into three groups according to biopsy reports: AHR, ACR or no rejection. The ACR group was further divided into early and late rejection (<90 and >90 days post-transplant, respectively). After a mean follow-up of 19 cases for 569 days, the incidence of AHR was 5.6% ($n=10$). Recipient pre-sensitization, delayed graft function, early rejection and higher creatinine at diagnosis were characteristic of AHR. Fourteen of 16 AHR patients were treated with PP and IVIG. One patient received only IVIG and another only PP. All AHR patients were given a steroid pulse, but only four received anti-lymphocyte therapy because of concomitant severe ACR. The ACR group comprised 43 patients. Graft survival by Kaplan Meier analysis was 81% and 84% in the AHR and ACR groups, respectively ($p=$NS). Outcomes were similar when AHR patients were compared with those with early ACR. The authors concluded that AHR when diagnosed early and treated aggressively with PP and IVIG carries a short-term prognosis that is similar to ACR.

Side effects, contraindications and interaction with other substances

IVIG is usually well tolerated with most adverse effects being mild and usually related to the rate of infusion. Serious hypersensitivity reactions such as

Table 3 Efficacy of IVIG in the management of RPL and other autoimmune disorders.

Reference and no. of patients	Disease	IVIG dose used	Outcome
Coulam and Goodman 2000 (42) 32 patients	RLP	500 mg prior to IVF/ET and the same rate per month until 28 weeks gestation	All patients had more than 12 IVF/ET failures with persistently high levels of CD56+/16+ cells. There was 56% success. Low CD56+/16+ NK cells associated with failure.
Stricker et al. 2001 (43)	RPL	200 mg/kg within 2 weeks of IVIG/IVF attempt and the same rate through 26–30 weeks of gestation	19/20 (95%) had successful term pregnancies. 7 of 11 women who refused IVIG became pregnant and all miscarried.
Kwak et al. 1996 (35)	RPL	400 mg/kg body weight for 3 days every 4 weeks plus anticoagulant therapy	86.3% success. NK activity, peripheral blood CD56+ and CD56+/16+ cells were suppressed 7 days post IVIG infusion.
Blanchette et al. 1994 (89) 34 patients	ITP	1000 /mg/kg body weight for 2 days	Both regimens effective but single dose of 800 mg/kg body weight given once offers faster recovery.
35 patients		300 mg/kg body weight given once	
Blanchette et al. 1993 (90) 9 patients with ITP affected fetuses	ITP	1000 mg/kg/week	Elevated fetal platelet count and prevented recurrence of antenatal intracranial hemorrhage.
	ITP	1000 mg/kg/day for two consecutive days	Platelet counts normalized in significantly fewer days when IVIG was used in combination with prednisone in comparison with no therapy or prednisone alone.
Singhi et al. 1999 (91) 22 patients	Severe GBS	400 mg/kg/day for 5 days (Sandoglobulin)	16 of 22 (72.7%) improved by at least one functional grade after 1 month and 15 (68%) were walking independently after 3 months compared with 2(18%) and 4 (36%) controls, respectively.
Boralevi et al. 2003 (92) 1 patient (3-year old boy)	Kawasaki	2000 mg IVIG and oral aspirin (60 mg/kg/day)	All symptoms disappeared and immediate follow-up was marked with guttate psoriasis.
Alekseeva et al. 2001 (93) 43 patients aged 4 to 15 years	SLE	300–1000 mg/kg day given daily or each other day	Treatment led to remission.
Wegner and Ahmed 2002 (94) 6 patients	Myasthenia gravis	Initial infusion of 400 mg/kg/day for 5 days followed with 400 mg/kg for 1 day every 3 to 4 months	Patients were treated effectively.
Huang et al. 2003 (95) 6 patients	Myasthenia gravis type II	400 mg/kg/day for 5 days	All patients improved beginning 1 to 9 days after initiation of treatment.

anaphylactic reactions occur only rarely and side effects occur in less than 5% of the people. These reactions include fever, vomiting, headache, shivering fits, dizziness, a nauseous feeling, itchy bubbles on the skin and skin nettle rash, high blood pressure, arthritis, back pain and anxiety (15). These symptoms attenuate or disappear when infusion rates are reduced or interrupted. A drop in blood pressure is rare, usually seen in 1:100 000, and patients with selective IgA deficiency can get anaphylactic shock. Accordingly, IgA-free, or reduced preparations of IVIG may be better in this respect (15). Patients with known side effects with other forms of therapies should therefore be treated prophylactically by corticosteroids intravenously 30 minutes before infusion of IVIG (15). The questions of hyperproteinemia and serum viscosity have been raised. Thus in one study, Steinberger et al. (97) evaluated the incidence of hyperproteinemia occurring after IVIG administration and its relationship to serum sodium, viscosity, osmolarity and serum osmolar gap. Eighteen IVIG infusions at a standard dose of 2000 mg/kg body weight administered over 2 to 5 days were evaluated. Paired t-testing revealed a statistically significant increase in serum protein and viscosity and a decrease in serum sodium and calculated osmolarity 24 hours after completion of therapy. These data demonstrate that increased viscosity occurs following IVIG therapy due to hyperproteinemia.

There may be oversensitivity to homologous immunoglobulins, especially if a selective IgA deficiency exists in addition to when anti-IgA antibodies are present. Also, a contraindication could exist in the case of diabetes due to high blood glucose, and in newborns or infants with fructose intolerance due to sorbitol increases (15). Care should therefore be taken in cases of pregnancy or breast feeding mothers. In cases where live virus vaccine is used, for example mumps, Rubella, variezella or measles, IVIG may neutralize the vaccine by suppressing activation of the immune system. Also, due to volume and half-life, passive administration of IVIG could lead to a false-positive serological antibody result for the vaccine. The time period between a living virus vaccination and IVIG should therefore be at least 3 months apart.

Discussion

Assuming that IVIG contains immune antibodies and physiological antibodies, immune antibodies would reflect the immunological experience of the donor

population and would be useful for replacement therapy and passive immunization, while natural autoantibodies would correct immune dysregulation. Efficacy is thought to result from a combination of mechanisms including inhibition of complement activation and binding to Fc receptors of macrophages and other killer leukocytes (Table 2). Given that autoimmune diseases have been associated with bacterial or viral infections (98, 99), which may trigger, sustain or accelerate disease, IVIG may efficiently eliminate such pathogens either by providing pathogen-specific immune antibodies and/or by natural first-line defense antibodies.

Although IVIG has been reported to limit the effects of idiotypic antibodies, it was shown in one study that high-dose IVIG accelerated clearance of autoantibodies but could only account for 20 to 40% of the decrease in autoantibody concentration after therapy (100). Such observations underline the need for further investigations to acquire a better understanding of the action mechanisms.

Outstanding differences in anti-hepatitis A and anti-cytomegalovirus antibody titers were shown when two lots of IVIG preparations from the USA (850 donor pool) and Europe (a 777 donor pool from Germany and Switzerland) were compared (32). There were also differences in anti-measles antibody titers in IVIG from non-remunerated plasma of European and American origin. These observations imply that the needs of immuno-deficient patients may be optimally covered when recipients of IVIG belong to the same population as the donors (32) and underline the basis for the differences in patient responsiveness to different IVIG preparations. These observations suggest that IVIG preparations from local plasma enriched with more immune antibodies to locally endemic pathogens may be therapeutically superior. It is on the basis of such observations that we propose that the donor population should reflect therapeutic needs of the target population or end users and that IVIG preparations be enriched with specific antibodies to common pathogens in the target population. Also donors should be limited to between 18 to 40 years of age in order to tap into the immunological capabilities of persons in this age bracket. We suggest that IVIG for use in RPL should include as donors women who have experienced RPL and whose sera demonstrate the capacity to inhibit CD56+/16+ NK cells.

Use of IVIG can be associated with a number of advantages. First, being of human origin it contains no chemicals and is therefore unlikely to have harmful teratological effects and does not require a specialized mechanism for its disposal from the body. In addition, being a product of pooled plasma implies natural protection to a wide spectrum of diseases. However, IVIG can potentially transmit bacterial and viral diseases, particularly hepatitis C, even though all plasma donors are tested beforehand for such infections. Also, a balanced suppression of the immune system and the risks of infection while dealing with exacerbation or crises where antibody titer may reach high levels must be addressed.

Retail cost may vary from one place to another but averages about 100 Euros per gram. Considering that a patient may need several weeks of IVIG at the rate of approx. 300–400 milligrams per day for management of patients with RPL or higher depending on the disease condition, IVIG is expensive and remains out of reach to a larger percentage of the world population, especially those in the developing world with inadequate health subsidies.

Conclusion

IVIG has proven to be effective in the management of a wide spectrum of diseases. Its use has been limited by high costs, poor understanding of the mechanisms of action and conflicting results presented in the literature regarding clinical efficacy. However, despite these uncertainties, the positive results obtained so far are undeniably promising and IVIG is presently seen as a valuable treatment option for several autoimmune diseases where patients may not respond to conventional therapies. In many of these cases, however, placebo-controlled studies are necessary to obtain a better understanding of the working mechanisms in order to facilitate development of rational treatment regimens.

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