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Intravenous Immune Globulins
A Review of Their Uses in Selected Immunodeficiency and Autoimmune Diseases

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Summary

Intravenous immune globulin (IGIV) was introduced a decade ago as a therapy for primary immunodeficiency diseases. It proved to be a valuable therapeutic substance for this purpose and is now considered to be the treatment of choice. The intent was to supply ubiquitous anti-infectious agent antibodies through passive immunisation to replace deficient circulating antibody content. During such therapy, unexpected benefits were noted in thrombocytopenic patients. Since that time, the therapeutic indications for IGIV infusions have greatly increased, with a particular interest in infectious, haematological and autoimmune diseases. This review summarises the status of IGIV therapy in haematological diseases within the categories of primary immunodeficiency diseases, secondary immunodeficiency states and autoimmune syndromes.

The majority of firm data have been gathered on the treatment of patients with primary immunodeficiency disease. These data are reviewed from the aspect of anticipated therapeutic response and side effects. Emphasis should be placed on the IgG circulating blood levels as there is a need for individualising therapy because of marked interindividual patient variation. The use of IGIV therapy in primary and secondary immunodeficiency states should consider the potential benefits to be attained in haematological malignancies and related complications which may be magnified by chemotherapy and radiation therapy. The mode of action of IGIV in autoimmune diseases, although not yet precisely determined, may involve establishing reticuloendothelial blockade or immunomodulation by supplying anti-idiotype antibodies.

Approximately 50 years ago, plasma was successfully fractionated to produce a number of relatively pure biologically active materials. Fraction II contained plasma γ-globulin, which was subsequently shown to be plasma antibody. This substance remained an interesting by-product of fractionation. In 1952 Bruton described a new disease, agammaglobulinaemia, characterised by the inability to produce circulating antibody (Dwyer 1984). Prophylactic intramuscular administration of fraction II, termed immune globulin, became the treatment of choice for patients having a deficiency of circulating antibody (Janeway & Rosen 1966). The intravenous route of administration was avoided because of severe and even catastrophic reactions (Baradnum et al. 1962; Dwyer 1984; Janeway 1970). Modification of the globulin molecule successfully reduced side effects, but the changed molecule had dubious clinical efficacy because of a shortened half-life (Jungi et al. 1986; Painter et al. 1965).

In 1979 the first successful use of an intravenous form of intact immune globulin (IGIV) was reported (Nolte et al. 1979). The IGIV had a low incidence of minor side effects and a normal half-life of approximately 25 to 28 days, and was shown to be therapeutically effective (Nolte et al. 1979; Pirofsky 1984). Since that time, second and third generations of IGIV have been developed, numerous worldwide commercial products have become available and IGIV therapy has become established as the treatment of choice for primary immunodeficiency diseases. More important has been the expansion of its therapeutic uses to include various secondary immunodeficiency states, autoimmune diseases and infectious complications in a variety of clinical states (Berkman et al. 1990; Good 1984; Morell & Nydegger 1986; Pennington 1986; Stiehm 1987).

1. Pharmacokinetics of IGIV

Commercially available liquid or lyophilised IGIV preparations are produced from human plasma obtained from large donor pools. A variety of different manufacturing processes are employed (Lundblad et al. 1987), including the use of polyethylene glycol, exchange chromatographic purification, acidification, and trace proteolysis and hydrolysis to dissociate IgG aggregation without cleaving the intact IgG molecule. Reaggregation is minimised by acidification (Pirofsky 1986, 1987) or the addition of sugars, glycine or albumin. The final product is almost entirely IgG with trace amounts of IgM and IgA. It is packaged to produce solutions ranging in concentration from 3 to 6%. Studies in our laboratories indicate that these preparations can be safely infused as 10 to 12% solutions.

The kinetics of IGIV are complex. The bulk of available data has been obtained for patients with primary immunodeficiency diseases and low serum levels of IgG. Such patients are extremely variable in both the production and catabolism of IgG (Buckley 1982; Nolte et al. 1979; Pirofsky 1984; Pirofsky et al. 1982). Accordingly, the data presented below must be interpreted within the limitations of such variability. An infusion of IGIV 200 mg/kg leads to an immediate elevation of serum IgG of approximately 2.5 to 3.0 g/L (Pirofsky 1984; Pirofsky et al. 1982). A 500 mg/kg IGIV infusion elevates serum IgG about 10 g/L (Montanaro & Pirofsky 1984). Within 24 hours, the increment of serum IgG obtained decreases 20 to 30%; 3 days after infusion, serum IgG increment decreases to about 50% of its peak levels. An additional 10% reduction of the increment occurs over the next 3 to 4 days. Thereafter, the drop in serum IgG is generally exponential, reflecting the half-life of the IGIV reagent (Nolte et al. 1979; Ochs et al. 1984; Pirofsky 1984). A return to baseline serum IgG levels generally occurs within 23 to 28 days of the infusion. A number of studies indicated the half-life of infused IgG ranged from 18 to 32 days (Ochs et al. 1986; Schiff 1986). It is of interest that high dose IGIV infusions resulting in immediate high levels of serum IgG appear to increase the rate of catabolism of serum IgG. These data clearly indicate that appropriate therapeutic infusion doses and schedules must be individualised for a specific patient.

2. *Therapeutic Use of IGIV in Haematological Disorders*

The impetus to develop intravenous immunoglobulin was the need to more effectively treat the haematological disorder agammaglobulinaemia. The demonstrated success of this therapeutic modality led to its trial in a variety of other clinical states (Berkman et al. 1990; Good 1984; Morell & Nydegger 1986; Pennington 1986; Stiehm 1987). This review will be limited to haematological disorders within the categories of primary and secondary immunodeficiency diseases and autoimmune disorders.

2.1 Primary Immunodeficiency Diseases

2.1.1 Indications

A wide variety of primary immunodeficiency diseases have been treated with IGIV including X-linked infantile agammaglobulinaemia, common variable hypoglobulinaemia, IgG deficiency with increased IgM, IgG subclass deficiences, Wiskott-Aldrich syndrome, ataxia telangiectasia, combined immunodeficiency diseases and transient hypogammaglobulinaemia in selected infants. In treating such patients, it should be emphasised that the expectations from IGIV treatment should not exceed its therapeutic role, restricted to the passive supply of IgG antibody. Thus, the early and vigorous prophylactic use of IGIV is the treatment of choice for X-linked agammaglobulinaemia, common variable hypoglobulinaemia and IgG deficiency with increased IgM. The indications for IGIV treatment in IgG subclass deficiency have not been established (Hill 1986). Patients with Wiskott-Aldrich syndrome may benefit when antibody synthesis is defective and thrombocytopenia is present. Similarly, patients with failure of antibody synthesis in ataxia telangiectasia may benefit from IGIV infusions. In patients with combined immunodeficiency diseases, IGIV therapy serves as a supplementary approach to more definitive therapies. The use of IGIV in transient hypogammaglobulinaemia is restricted to infants suffering from infectious complications of the immunodeficiency.

The development of IGIV was in response to the need for improved treatment of infantile X-linked and common variable agammaglobulinaemia (Cunningham-Rundles et al. 1984; Nolte et al. 1979). Prior studies indicated that intramuscular immune globulin was beneficial (Janeway & Rosen 1966). However, appropriate therapeutic regimens could not be established due to limitations imposed by the volume required for the therapeutic bolus, the pain of such injections and the lack of acceptance by both patient and physician of these disadvantages (Nolte et al. 1979). The initial report of IGIV use in these diseases clearly indicated that appropriate dosages and schedules of infusions could be administered, and both improved resistance to infection and almost universal patient and physician satisfaction would result (Nolte et al. 1979). These initial results have been amply confirmed and IGIV therapy has replaced the intramuscular route as the treatment of choice (Cunningham-Rundles et al. 1984; Good 1984; Morell & Nydegger 1986; Pennington 1986).

2.1.2 Dosage Considerations

It is less clear as to the appropriate dosage and administration schedule. Dosages of 100 mg/kg IGIV every 4 weeks appear to confer benefits equal to those achieved by intramuscular therapy (Ammann et al.1982). At 150 mg/kg IGIV every 4 weeks, freedom from infection is greater than that seen with intramuscular therapy (Nolte et al. 1979). At dosages substantially higher than 400 mg/kg IGIV every 4 weeks, some observers claimed improvement of pulmonary function and reversal of the course of bronchiectasis (Bernatowska et al. 1987; Roifman et al. 1987). Many physicians use 200 mg/kg IGIV every 4 weeks with appropriate antibiotics as the minimal therapy (Pirofsky 1984). With this dosage, pulmonary function almost always improves and irreversible pulmonary disease does not develop; in such cases, the higher doses are not required.

The variability in IgG production and catabolism makes it impractical to focus on a dosage and schedule appropriate for all patients. Rather, each patient shgould be studied individually, with the

serum IgG level as the critical factor to be determined. Serum IgG levels should be maintained at 4 g/L or higher during the treatment period, although there is little evidence that increases of the serum IgG trough level above 3.5 g/L leads to enhanced resistance to infectious complications (Ochs et al. 1984). Further, there is no evidence that IgG trough levels raised even to normal IgG values can reverse anatomical damage and scar formation in the lungs, ears, sinuses, etc. High dose levels of IGIV do not appear to have any adverse effects compared with a standard 200 mg/kg IGIV dose. However, the cost (US$35.00/g to the pharmacy, US$70.00/g to the patient in the US) makes it prudent to reserve high dose therapy for those few patients who do not respond well to the standard 200 mg/kg IGIV every 4 weeks. A dosage of 100 to 150 mg/kg IGIV every 2 weeks self-administered in a home setting (Ashida & Saxo 1986; Ochs et al. 1986) may be satisfactory both therapeutically and psychologically for the majority of patients. Patients should be treated in a physician-supervised setting with a serum IgG level drawn before an infusion of IGIV for at least 4 months before the use of a specific dose, infusion schedule and home administration setting are elected.

2.1.3 Adverse Effects

Reactions to present IGIV preparations are minimal and generally restricted to mild discomfort. Although more common during the first 2 infusions and in the presence of active infection, such reactions appear to be primarily related to the speed of infusion. The majority of reactions are 'vasomotor' or 'anaphylactoid' in nature. Common findings include pallor, sweating, nausea, vomiting, chills, low grade fever, muscle aches or pains, back discomfort, tachycardia, elevation or reduction of blood pressure and chest tightening (Pirofsky 1984). When infusions are given over a 1- to 3-hour period, the incidence of reactions is less than 5% and occur during the infusion; when infusions are given rapidly (< 30 minutes) the reactions may appear soon after completing the infusion. Temporary slowing or stopping of the infusion leads to a disappearance of complaints within 15 to 30 minutes, and the infusion may be completed at its normal rate. Termination of the infusion is generally not indicated. Rarely, a true anaphylactic reaction will occur due to IgE anti-IgA (Burks et al. 1986). In such cases, the infusions should be terminated and appropriate therapy initiated.

2.2 Secondary Immunodeficiency Diseases

The success of IGIV therapy in the primary immunodeficiency diseases suggests the potential for a similar beneficial effect in the secondary varieties. As in the primary forms, the intent is to replace deficient circulating antibody by passive immunisation. A reduced circulating antibody content is not uncommon in malignancies and this tendency is magnified by vigorous chemotherapy and radiation therapy treatments resulting in severe infectious complications. Three major haematological entities within this group have been evaluated: chronic lymphocytic leukaemia, plasma cell myeloma and bone marrow transplantation.

2.2.1 Chronic Lymphocytic Leukaemia

A prospective, double-blind, randomised IGIV-placebo study was performed in 84 patients with chronic lymphocytic leukaemia (Besa 1984; Cooperative Group 1988). The subjects were stratified as to disease stage and IgG levels ($\gtrless$ 4.0 g/L) and 400 mg/kg every 3 weeks of placebo or IGIV was administered. A 50% reduction in bacterial infections from that seen in placebo patients and an increased probability of remaining bacterial infection-free was found in the IGIV recipients. A small crossover study was performed and again IGIV therapy was found to be beneficial (Griffiths et al. 1989). Infections of moderate severity were primarily prevented. Minor and severe bacterial infections and viral infections were not influenced by IGIV therapy.

2.2.2 Plasma Cell Myeloma

The ability of IGIV therapy to reduce infectious complications in plasma cell myeloma has also been investigated (Gordon et al. 1984; Schede 1986). It was demonstrated that elevations in serum IgG

levels occurred with IGIV administration. One prospective crossover study in 94 patients with plasma cell myeloma reported a substantial reduction in bacterial infections (Schede 1986). The use of IGIV therapy in plasma cell myeloma may be limited by increased catabolism of infused IgG in the presence of high levels of circulating IgG. These data and the above findings in chronic lymphocytic leukaemia suggest that IGIV therapy may be beneficial in other haematological malignancies, particularly when extensive chemotherapy and radiation therapy are used.

2.2.3 Bone Marrow Transplantation

Infectious diseases, particularly cytomegalovirus (CMV) infections and interstitial pneumonia, are lethal complications of bone marrow transplantation. The infectious agent is either introduced by blood transfusions or in the graft, and/or may be latent in the recipient. The potent immunosuppression required to preserve the graft can activate the virus, leading to severe and even fatal CMV infections. In particular, interstitial pneumonia may occur. Immune globulin therapy has been used in the form of infusions of plasma from individuals having high antibody titres to CMV (Winston et al. 1982), by conventional IGIV infusions (Meyers et al. 1983; Winston et al. 1983) and with hyperimmune CMV IGIV (Condie & O'Reilly 1984). These studies indicate that prophylactic IGIV does not prevent CMV infections. The use of CMV seronegative blood and CMV seronegative donor-recipient pairs is most crucial in this respect. However, IGIV therapy markedly reduces the risk of CMV pneumonia and death, as well as Gram-negative and local infections.

Preliminary data suggest that IGIV alone or combined with ganciclovir may be beneficial in treating active CMV infections and interstitial pneumonia (Blacklock et al. 1985; Emanuel et al. 1988; Nicholls et al. 1983; Reed et al. 1988). A surprising observation has been made in patients undergoing bone marrow transplantation and receiving IGIV therapy. When prophylactic IGIV therapy was used, reduced incidence of acute graft versus host disease (GVHD) resulted (Sullivan et al. 1988; Winston et al. 1987). It is unlikely that identical mechanisms are involved in preventing the progression of CMV infection into interstitial pneumonia and acute GVHD in the bone marrow transplant recipient. Rather, it is likely that the anti-GVHD effect is related to the immunomodulation capacity of IGIV.

2.3 Autoimmune Diseases

2.3.1 Idiopathic Thrombocytopenic Purpura

While treating the hypogammaglobulinaemia of a patient with Wiskott-Aldrich syndrome with IGIV, Imbach and colleagues (1981) noted that the associated thrombocytopenia was rapidly corrected. The study was expanded to evaluate 11 patients with acute or chronic idiopathic thrombocytopenic purpura (ITP). A dosage of 400 mg/kg IGIV daily for 5 days was given and all patients improved in their thrombocyte levels. This observation has been amply confirmed by many investigators (Bussel et al. 1983; Bussel & Pham 1987; Imbach et al. 1985; Newland 1987). The therapeutic dosage of IGIV varied within a narrow range and a usual course of therapy consisted of 2.0 g/kg IGIV administered in divided doses over 2 to 5 days. The majority of patients with ITP that responded exhibited a rapid response to IGIV therapy. The therapeutic effect may be noted within 1 to 5 days and the level of thrombocytes attained is sufficient to prevent bleeding problems. Whether such therapeutic effects are sustained, however, is highly variable.

Several broad parameters for anticipated responses are available, including the acute or chronic nature of the disease process and whether the patient is an adult or a child. In general, children exhibit the best response and such patients with acute ITP have the greatest probability of maintaining a sustained response. Accordingly, a child with acute ITP may be the best candidate for IGIV therapy. It should be emphasised, however, that this type of patient has the highest incidence of untreated spontaneous remission of ITP. Therefore, it is suggested that IGIV therapy be reserved for patients with thrombocyte levels below 20 000/

mm^3 and, thus, in potential danger of intracranial haemorrhage. In contrast, adult patients with chronic ITP have the poorest immediate, sustained and repeated thrombocyte response rate after IGIV therapy. It is apparent that the decision concerning whether to use IGIV therapy and when must be individualised. Factors to be considered include the requirement for a rapid therapeutic effect, delayed therapeutic or toxic side effects of corticosteroids, the possibility of avoiding the need for a splenectomy and its subsequent irreversible induction of susceptibility to infection, preoperative protection, protection of the fetus in the presence of maternal ITP and the need for adjunct therapy in the presence of haemorrhage. Also, the cost-effectiveness of IGIV therapy must be compared with the cost of a splenectomy, immunosuppressive therapy, prolonged corticosteroid therapy and hospitalisation.

The mode of action of IGIV in ITP is still to be determined. It is unlikely, however, that passive immunisation in the classical sense is the major mechanism. There is a possibility that the antibody content of the IGIV causes the elimination of an as yet unidentified infectious agent responsible for the ITP. The unexpected therapeutic effect of IGIV in ITP has expanded the search for other mechanisms which may be responsible. A number of possibilities has been investigated including blockade of the reticuloendothelial system mediated by the Fc portion of the immunoglobulin molecules, immune modulation through supply of anti-idiotype antibody, other mechanisms of immunomodulation, reduction of autoantibody formation by anti-idiotype antibody and feedback inhibition of antibody formation (Bussel & Hilgartner 1984; Clarkson et al. 1986; Dammacco et al. 1986; Imbach & Jungi 1983). Current thinking suggests that reticuloendothelial blockade and anti-idiotype antibody immunomodulation are the principal mechanisms in the correction of ITP by IGIV infusion.

2.3.2 Other Thrombocytopenic States

The therapeutic action of IGIV in ITP has stimulated a number of studies in nonimmune forms of thrombocytopenia. Mixed results were reported in patients having thrombocytopenia due to chemotherapy (Kekomaki et al. 1984; Schiffer et al. 1984) and as a part of severe aplastic anaemia (Becton et al. 1984; Kurtzberg et al. 1987). In addition, several placebo-controlled studies in patients refractory to donor platelet infusions reported limited and transient therapeutic responses (Ziegler et al. 1987). The limited data available are insufficient to establish either the dosage schedule or the true value of IGIV therapy in these conditions.

A logical extension of the IGIV-ITP observations was the expansion of the IGIV therapeutic approach to other immune mediated haematological cytopenias. A number of studies reported a therapeutic response to IGIV therapy in patients with neonatal neutropenia and thrombocytopenia with maternal systemic lupus erythematosus (Hanada et al. 1987), in chronic lymphocytic leukaemia patients with autoimmune thrombocytopenia or anaemia (Besa 1984), in patients with antibody-mediated red cell aplasia and pancytopenia (Clauvel et al. 1983) and in patients with autoimmune neutropenia (Bussel et al. 1983, 1988; Pollack et al. 1982). Insufficient studies have been performed to fully evaluate the potential of IGIV therapy in these conditions. More extensive studies have been done on patients with autoimmune haemolytic anaemia (Mueller-Eckhardt et al. 1985; Richmond et al. 1987; Salama et al. 1987), although variable results were obtained. Failure of this therapy was not unusual; in contrast, however, rapid and frequent dramatic therapeutic responses have also been observed.

IGIV therapy may be beneficial in these immune mediated cytopenic states when its mechanism of action is fully understood, allowing the choice of appropriate subjects. Variables such as the immune globulin class of the autoantibody and the method by which cell destruction is initiated may be crucial to the therapeutic effect. Schreiber (1990) has suggested that IgG cell surface antibody leads to cell destruction in the spleen and IGIV therapy may be therapeutic by reticuloendothelial blockade. In contrast, IgM-mediated cell destruction may not benefit from IGIV therapy. Other observers feel that immunomodulation by anti-

idiotype antibody (Rosen & Wedgwood 1989), as seen in Kawasaki disease (Leung 1989) and other autoimmune states (Imbach & Morell 1989; Mannhalter & Eibl 1989; Schwartz 1989), is the critical mechanism through which IGIV initiates its effect.

The treatment of patients with factor VIII deficiencies may be complicated by the development of autoantibodies against the critical coagulation factors which are therapeutically infused. After IGIV administration, many of these patients have a decrease in titre of the autoantibody to factor VIII and an increase in their plasma factor VIII activity (Green & Kwaan 1987; Kazatchkine et al. 1989; Sultan et al. 1984; Zimmerman et al. 1985). It has been demonstrated that IGIV is bound to antibody against factor VIII. Accordingly, it is most probable that factor VIII acts as an antigen and IGIV contains anti-idiotype antibody to the shared idiotype. In this fashion, IGIV competes with and suppresses the synthesis of autoantibody. One study suggested that tolerance to factor VIII in these patients may be induced by introducing IGIV (anti-idiotype antibody), antigen (factor VIII) and cyclophosphamide (Nilsson et al. 1988). A similar mechanism of IGIV anti-idiotype antibody action is postulated for the therapeutic effect of IGIV seen in myasthenia gravis with anti-acetylcholine receptor antibodies (Arsura et al. 1986).

3. Conclusions

In diseases characterised by inadequate amounts of circulating serum antibody, either of a primary or secondary variety, IGIV infusions have clearly become the therapy of choice. Passive immunisation using IGIV has proven to be beneficial in both a prophylactic schedule and as an immediate therapy in the presence of active infections. Currently available IGIV preparations are produced from large quantities of normal plasma, supplying a mixed pool of antibodies. In the future, antibody-specific IGIV may also become available through the fractionation of hyperimmune plasma. This may supply a more specific and potent therapeutic tool for specific infectious complications.

If the concept of an anti-idiotype network maintaining immunomodulation and the prevention of autoimmune disease is correct, IGIV may assume major therapeutic roles in a variety of immune mediated diseases (Rosen & Wedgwood 1989). All humans must produce and maintain a large population of circulating anti-idiotype antibody in their normal physiological state. Plasma pools, obtained from large numbers of normal donors, would represent a valuable supply of ubiquitous anti-idiotype antibodies and the classically considered circulating antibodies against infectious agents. Immune globulin could therefore be a potent therapeutic tool for the treatment of immune mediated diseases, particularly the autoimmune varieties. IGIV preparations specifically produced for their anti-idiotype antibody content may be required and developed in the future for such new therapies.

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