ARTICLE

Recommendations for the use of immunoglobulin therapy for immunomodulation and antibody replacement

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Polyvalent immunoglobin, derived from pooled human plasma, can be administered via the intravenous, subcutaneous or intramuscular route. Therapy is standard of care in the treatment of a number of immune-mediated pathologies across disciplines. By volume, the majority is used in neurology (~40%). In primary immunodeficiencies, therapy reconstitutes humoral immunity at replacement doses (0.4 - 0.6 g/kg/month), decreasing infections, and is usually lifelong. However, high doses, usually 2 g/kg total dose over five days, are required for immunomodulation in autoimmune and inflammatory indications. A high-quality evidence base supports use in primary antibody failure, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, acute idiopathic thrombocytopenia, Kawasaki disease and immunobullous diseases. Low-quality evidence shows benefit in many other uncommon autoimmune and immunodeficient conditions. In South Africa, use of immunoglobulin therapy is restricted and, given the cost involved, will likely remain so. Therefore, the incremental benefit over other forms of immunosuppression, particularly corticosteroids, must be assessed carefully on a case-by-case basis. In most cases, therapy will be second-line or ‘rescue’ and motivation will be required. This short review aims to provide clinicians with the necessary understanding of the therapy, general considerations for use, and evidence base and quality thereof for well-established indications.

Table 1. Current major uses and grade of evidence for immunoglobulin therapy

<table>
<thead>
<tr>
<th>Neurology</th>
<th>Haematology</th>
<th>Immunology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barré syndrome (A)</td>
<td>Immune thrombocytopenic purpura (RCT, limited evidence in chronic ITP) (A)</td>
<td>Primary antibody deficiencies (A)</td>
<td>Kawasaki disease (A)</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy (A)</td>
<td>Allimmune thrombocytopenia (feto-maternal/neonatal)</td>
<td>Specific antibody deficiency (GPP)</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome (no mortality benefit)</td>
</tr>
<tr>
<td>Multifocal motor neuropathy (GPP)</td>
<td>Haemolytic disease of the newborn</td>
<td>Secondary antibody deficiency (including myeloma, CLL (RCT), drugs and other causes) (GPP)</td>
<td>Immunobullous disease (A)</td>
</tr>
<tr>
<td>Myasthenia gravis (GPP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis/polymyositis (GPP)</td>
<td>Autoimmune haemolytic anaemia (GPP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune limbic encephalitis (GPP)</td>
<td>Post bone marrow transplantation (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiff person syndrome (GPP)</td>
<td>Parvovirus B19-associated aplasia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial; ITP = immune thrombocytopenia; CLL = chronic lymphocytic leukaemia.

*Grading of Recommendations Assessment, Development and Evaluation (GRADE) to rate quality of evidence in accordance with Cochrane reviews: [A] = level A or established evidence-based RCT, ‘Good practice point’ (GPP) refers to current consensus opinion in the absence of level A evidence.

†Anti-N-methyl-D-aspartate, anti-voltage-gated potassium channel antibody positive.
Mechanisms of polyvalent immunoglobulins action to prevent infections
Key role for treatment of primary and secondary immunodeficiency

- **Opsonisation**
  - IgG facilitates bacterial uptake
  - Phagocyte

- **Neutralisation**
  - IgG
  - Bacterial toxins
  - Cell with toxin receptors

- **Complement activation**
  - Cell lysis
  - Formation of membrane attack complex

Suggested immunomodulatory mechanisms of polyvalent immunoglobulins
Key role for treatment of autoimmune pathology

- **Blocking of cellular and complement receptors**
  - Complement receptor
  - Monomeric IV Ig

- **Autoantibody, cytokine neutralisation**
  - Cytokine
  - Autoantibody
  - Anaphylatoxin scavenging to reduced pro-inflammatory milieu

- **Saturation of FcRn decreasing autoantibody half-life**
  - Endothelial cell
  - IV Ig dimer

- **Modulation of balance between inhibitory and activating FcγR expression**
  - Plasma cell
  - Antigen

- **Blocking of activating FcγR**
  - IV Ig dimer

- **Expansion of Treg cells**

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Fig. 1. Established and proposed mechanism of action for immunoglobulin therapy (ADCC = antibody-dependent cell-mediated cytotoxicity; FcRn = Fc neonatal receptor; FcγR = Fcγ receptor; IgG = immunoglobulin G; IV Ig = intravenous immunoglobulin; Treg cells = regulatory T cells.)
Immunoglobulin therapy: General considerations

Polyvalent immunoglobulin is purified from pooled human plasma. This origin as a plasma product underpins the majority of general considerations, both advantages and disadvantages.

Manufacture and available preparations

Fractionation of immunoglobulin from donor plasma, removing unwanted and/or infectious substances and stabilising and packaging it for remote clinical use, is a laborious and expensive process. Only four registered products are available in SA (Table 2). Immunoglobulin preparations are available for intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration, with concentrations between 2% and 16%. SC administration is increasingly used for both immunomodulation (high dose) and replacement therapy. Product differences warranting clinical considerations, highlighted for SA products in Table 2, include varying immunoglobulin (Ig) A content, different stabilising sugars/amino acids, storage conditions and cost.

Mechanisms of action

The pooling of antibodies from thousands of donors provides a diversity of antibody repertoires and specificities. Fig. 1 outlines proposed mechanisms of actions. In immunodeficiency, antibody replacement therapy reconstitutes fundamental humoral immunity. Immunomodulatory mechanisms of action are less well understood and are likely to differ, depending on the specific autoimmune pathogenesis and individual genetic background. Diseases responding rapidly, but with short-lived duration of efficacy, suggest that high serum levels of therapeutic IgG ‘neutralise’ pathogenic autoantibodies. Otherwise proposed mechanisms include binding or blocking of the antigen-binding site (anti-idiotype), enhancing IgG turn-over, thereby reducing circulating pathogenic IgG, as well as scavenging circulating complement binding sites and interfering with activation of the complement cascade. Two excellent reviews discuss the immunomodulatory mechanism of action in greater depth.

Side-effects

The major side-effects of immunoglobulin preparations are summarised in Table 3. Immediate infusion-related reactions occur in about 1% of all IV Ig infusions, but are usually mild and can be treated symptomatically with simple analgesia. Moderate reactions can be treated with antihistamines or corticosteroids. Reactions usually relate to intercurrent infections or over-rapid administration and can be avoided with brief clinical review prior to therapy, slow initiation of therapy and adherence to manufacturers’ suggested infusion rates. However, the more serious side-effects are associated with high-dose IV Ig and relate to the up to fourfold increase in serum IgG and additional plasma proteins. One needs to monitor for renal impairment, which is usually reversible. Pre-hydration is important and it is preferable to use an IV preparation without sugars or the SC route of administration in patients with pre-existing renal disease or the elderly. Unfortunately, the choice of product options is currently limited in SA.

Therapeutic use: Evidence and current application in SA

Immunoglobulin use is supported by high-quality evidence (randomised control trials (RCTs)) for certain conditions in neurology, haematology, immunology and dermatology (Table 1). In addition, Ig therapy is used off-label, and with limited evidence, for a wide array of other diseases with immunopathology, usually after the failure of first-line therapies. Globally, and in SA, the largest volume of Ig is used by neurology (~40%), followed by haematology. In immunodeficiencies, immunoglobulin replacement is used in lower volumes but therapy tends to be lifelong. The high cost of therapy and lack of availability limit use worldwide, but in SA, especially in the public sector, this affects use – even for conditions with well-established benefit. In the sections below we outline the evidence by discipline. Table 4 provides important general considerations and practice points prior to commencing immunoglobulin therapy.

Neurology

Ig therapy is highly effective in a number of neuromuscular diseases, but the substantial cost must be considered in developing a treatment plan. The mechanism of action of Ig in different diseases may vary and therefore appropriate dosing and frequency of administration may differ. Cochrane reviews provide good evidence that recovery in severe Guillain-Barré syndrome is hastened if IV Ig (0.4 g/kg for 5 days) or plasma exchange are started within the first two weeks of symptom onset. There is no evidence that giving IV Ig after plasma exchange provides additional benefit. In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), IV Ig (one course, total dose 2 mg/kg) is superior compared with no treatment in inducing improvement within six weeks; for every three persons treated with IV Ig, one improved. However, similar clinical benefits were obtained at two and six weeks when IV Ig was compared with plasma exchange or corticosteroids (prednisone or IV methylprednisolone). Despite limited data, one trial showed sustained benefit for 24 and 48 weeks using IV Ig compared with placebo. Compared with IV methylprednisolone (0.5 g x 4 days, monthly), those receiving monthly courses of Ig for CIDP were less likely to discontinue owing to lack of efficacy or intolerance, but were more likely to worsen after discontinuation at 6 months. Overall, current evidence suggests that either IV Ig or corticosteroids should be considered as first-line treatment for CIDP. If doses of the aforementioned induction treatment are required to remain high to maintain disease control, an additional immunosuppressant or immunomodulating treatment should be considered. In the rare case of multifocal motor neuropathy (MMN) that does not respond to prednisone or plasma exchange, IV Ig therapy should be considered based on limited evidence; however, not all patients show substantial responses and ongoing therapy should be re-evaluated regularly. Based on limited evidence, IV Ig resulted in a modest, short-term benefit in IgM anti-myelin-associated glycoprotein paraproteinemia demyelinating neuropathy. There are no RCTs to support the use of IV Ig in paraneoplastic neuropathies, diabetic amyotrophy or radiculopexopathies, vasculitic neuropathies or painful neuropathies associated with SJögren’s syndrome.

Based on RCTs, IV Ig (and plasma exchange) is effective in treating acute crises or severe worsening of myasthenia gravis (MG), with clinically relevant effects on average after 4 - 7 days. IV Ig shows no effect on mild to severe but stable MG. There is no evidence to support the use of IV Ig in inclusion body myositis. Based on one RCT, IV Ig may be considered as additional immunosuppressive therapy in severe or life-threatening dermatomyositis and probably also in polymyositis despite the absence of RCTs.

Although a number of older RCTs using IV Ig in relapsing-remitting multiple sclerosis showed a reduction in relapse rates, these effects were not consistently accompanied by a reduction in brain lesions on magnetic resonance imaging. Currently, IV Ig may be indicated to reduce relapses during pregnancy and breastfeeding when the standard disease-modifying drugs are contraindicated. One RCT showed IV Ig was of benefit in severe stiff person syndrome, with benefits lasting between six weeks and one year. In the increasingly...
recognised antibody-mediated limbic encephalitis, most frequently due to N-methyl-D-aspartate (NMDA)-receptor antibodies, observations from a large cohort (N=577) suggest that steroids as well as plasma exchange or IV Ig may have a place as first-line therapy; about half of the patients responded within four weeks and did not require second-line therapies.[17]

One RCT found no efficacy in using IV Ig as add-on therapy in refractory epilepsy when compared with placebo.[18]

**Haematology**

Treatment with Ig has been found to be useful in a number of haematological disorders. Immune thrombocytopenia (ITP) remains a poorly understood disorder, where antibodies to platelet antigens lead to clinically significant platelet destruction that is not compensated by bone marrow production. The acute presentations are common in children, while chronic forms are dominant in adults. Although the initial treatment of ITP remains corticosteroids (prednisone 1 - 2 mg/kg), intravenous immunoglobulin at 0.5 - 2 g/kg has similar efficacy and was found to be cost-effective in children.[19]

In adults, immunoglobulin therapy remains a second-line treatment, mainly owing to cost, but is particularly useful to induce a more rapid response in emergency situations (active bleeding, need for procedures or surgery); however, most responses are transient.[20]

Overall, the effectiveness of this treatment is similar to that of corticosteroids, which are significantly cheaper. IV Ig is indicated in patients with thrombocytopenia secondary to HIV infection unresponsive to antiretroviral therapy, and the management should not differ from that for the idiopathic form.[21,22]

Immune red cell destruction has also been a focus of interest for immunoglobulin therapy. Controlled studies have
suggested a reduction in parameters of red cell breakdown in ABO and Rh haemolytic disease of the newborn, although larger prospective studies are required. Some retrospective data also support its use in fetal red cell alloimmunisation, although a meta-analysis was unable to confirm this. Immunoglobulin therapy was found to be effective in IgG-mediated immune haemolytic anaemia in only 40% of patients and is not considered as first-line therapy, where corticosteroids are more effective. However, immunoglobulin therapy may be more active in combination with steroids, where a more rapid response is observed. Anecdotal data suggest that the combination was also useful in hyper-immunoglobulinemia syndrome associated with sickle cell anaemia in the context of intense red cell breakdown with the non-reactive direct antiglobulin test. Pure red cell aplasia (PRCA) is characterised by severe anaemia with absent maturing red cell precursors in the marrow and reticulocytopenia. Viral infections, particularly B19 parvovirus, are a common cause of PRCA, especially in patients with HIV infection or who are immunosuppressed following organ transplantation. Immunoglobulin therapy is particularly effective in this group at standard doses, with universal responses observed within 90 days of therapy.

Immunoglobulin therapy has been recommended in other situations, such as after allogeneic stem cell transplantation for the prevention of cytomegalovirus reactivation, although no controlled studies are available; however, a phase II study and retrospective review by Ichihara et al. showed equal viral reactivation rates compared with the untreated group. Similarly, while anecdotal cases suggested effectiveness in acquired haemophilia or Von Willebrand’s disease, review of the available evidence does not support this approach. IV Ig may be reserved for patients with hypogammaglobulinaemia (IgG <4 g/L) after bone marrow transplantation and in adults with secondary antibody deficiency associated with chronic lymphocytic leukaemia and myeloma, although its cost-effectiveness has been questioned.

### Table 3. Immunoglobulin therapy – adverse reactions

<table>
<thead>
<tr>
<th>Adverse reaction and frequency*</th>
<th>Severity</th>
<th>Route of administration</th>
<th>Onset from infusion†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (20 - 40%)</td>
<td></td>
<td>IV Ig</td>
<td>SC Ig</td>
</tr>
<tr>
<td>Infusion site pain, swelling, erythema (up to 75% in SC Ig)</td>
<td>Usually mild</td>
<td></td>
<td>Usually immediate</td>
</tr>
<tr>
<td>Anxiety, malaise, fatigue</td>
<td>Usually mild</td>
<td></td>
<td>Usually immediate</td>
</tr>
<tr>
<td>Myalgia, arthralgia, back pain</td>
<td>Usually mild</td>
<td></td>
<td>Usually immediate</td>
</tr>
<tr>
<td>Fever, chills, flushing</td>
<td>Usually mild</td>
<td></td>
<td>Usually immediate</td>
</tr>
<tr>
<td>Tachycardia, hypo-/hypertension</td>
<td>Usually mild</td>
<td></td>
<td>Usually immediate</td>
</tr>
<tr>
<td>Headache</td>
<td>Mild to moderate</td>
<td>IV Ig &gt;&gt; SC Ig</td>
<td>Immediate, but can be delayed</td>
</tr>
<tr>
<td>Less common (&lt;5%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>Moderate</td>
<td>IV Ig &gt;&gt; SC Ig</td>
<td>Delayed</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Moderate</td>
<td>IV Ig only</td>
<td>Delayed</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Mild/transient</td>
<td></td>
<td>Delayed</td>
</tr>
<tr>
<td>Interference with vaccine effectiveness and/or immunodiagnosis</td>
<td>N/A</td>
<td>IV Ig = SC Ig</td>
<td>N/A</td>
</tr>
<tr>
<td>Eczema</td>
<td>IV Ig</td>
<td></td>
<td>Delayed</td>
</tr>
<tr>
<td>Rare (&lt;0.1%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>Severe</td>
<td>IV Ig &gt;&gt; SC Ig</td>
<td>Immediate</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Severe</td>
<td>IV Ig</td>
<td>Late</td>
</tr>
<tr>
<td>Blood-borne infectious disease</td>
<td>Severe</td>
<td>IV Ig = SC Ig</td>
<td>N/A</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Mild to severe</td>
<td>IV Ig=SC Ig</td>
<td>Delayed</td>
</tr>
</tbody>
</table>

1. IV Ig = intravenous immunoglobulin therapy; SC Ig = subcutaneous immunoglobulin; N/A = not applicable.
2. Frequencies are for patients using long-term therapy. Table modified from Piller and Chapel.
3. Time of onset of adverse reaction from start of infusion, immediate: within 6 hours; delayed: 6 hours to 1 week; late: weeks to months.
4. With the exception of anaphylactic reactions, the less common and rare side-effects tend to occur with the higher immunomodulatory doses of immunoglobulin.

**Immunology**

Replacement immunoglobulin therapy is life-saving and cost-effective for patients with severe hypogammaglobulinaemia/ agammaglobulinaemia owing to primary immunodeficiencies, such as common variable immunodeficiency (CVID) and X-linked agammaglobulinaemia. However, treatment is less clear-cut for the spectrum of borderline hypogammaglobulinaemia, specific antibody deficiency or subclass deficiencies. In these cases, demonstration of absent or declining functional antibody responses, i.e. to test vaccination, in the context of documented ongoing infections, should warrant a 12-month trial of therapy with regular review of clinical response. In long-term replacement therapy, clinicians should focus on two fundamental components: (i) ensuring adequate dosing to prevent infections; and (ii) optimising and monitoring product and patient factors to ensure ongoing compliance, efficacy and safety.

Most national guidelines recommend a starting dose of 400 - 600 mg/kg/month, with higher doses for patients with structural lung damage, e.g. bronchiectasis. Maintenance of adequate serum levels is critical to prevent serious bacterial infections. Pneumonia incidence with IV Ig therapy is five times higher at a trough IgG level of 5 g/L compared with 10 g/L. A meta-analysis of multiple studies found a 27% decline in pneumonia incidence for each 1 g/L increase in trough IgG. A similar relationship is seen with subcutaneous immunoglobulin (SC Ig) therapy. Ensuring adequate trough levels is cost-effective. Increasingly, clinicians and funders are treating towards a patient’s ‘biological’ trough level which, similar to the normal range of serum IgG in healthy people,
recognises that individuals may require differing trough IgG levels to prevent a similar number of infections. At treatment initiation, patients should be reviewed by a medical specialist every 2 - 3 months, with monitoring of efficacy, serum IgG and infusion-related issues, but once treatment has been established six-monthly review is recommended.[32]

Chronic therapy with immunoglobulin is expensive, logistically challenging and disruptive to patient lifestyle. To improve long-term compliance, physicians should involve patients and their families early in discussions about route of administration (IV Ig versus SC Ig), timing and location of therapy (clinic-based versus home-based) as well as funding. Involvement of a specialist nurse for home infusion training and follow-up monitoring is important. National patient support groups, such as the Primary Immunodeficiency Network of South Africa (PINSa, http://pinsa.org.za/), offer patients much-needed additional support as well as a role in national advocacy. In SA, the majority of children and adults with primary immunodeficiency receive hospital-based IV Ig replacement therapy, often at suboptimal doses because of cost constraints. However, many developed countries have increasing numbers of immunodeficient patients performing home-based IV Ig or SC Ig therapy.[33] This could potentially be applied in SA, but would require a substantially strengthened specialist nursing and patient support infrastructure to ensure safety and efficacy.

A more in-depth discussion on the issues around immunoglobulin replacement therapy for immunodeficiency has recently been published.[32]

Use in other disciplines
Immunomodulation with IV Ig is also used in a number of other disciplines and specific conditions. In the majority of these it is used as ‘rescue’ therapy after the failure of first-line treatment, usually consisting of corticosteroids and a steroid-sparing immunosuppressant. In dermatology, IV Ig is used globally for blistering skin diseases. RCT data support the use of IV Ig for steroid-resistant pemphigus and pemphigoid, with a single course of a 0.4 g/kg dose for 5 days significantly reducing disease activity.[32] However, although widely used, pooled analysis shows no mortality benefit for use in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis.[34] IV Ig is a well-established first-line therapy for Kawasaki disease to prevent new coronary artery abnormalities, with high-quality evidence supporting use of a single 2 g/kg dose within 10 days of symptom onset.[35] Combination with corticosteroids may offer additional benefit.[36] There is limited evidence of benefit in other autoimmune vasculitides, or catastrophic antiphospholipid syndrome, and IV Ig is not currently recommended over less expensive therapy.[37] Large numbers of studies have examined the use of IV Ig and IgM-enriched immunoglobulin preparations for the treatment of severe bacterial sepsis and septic shock, and pooled data fail to show a mortality benefit.[38] In preterm (<37 weeks) and low-birthweight infants, IV Ig replacement can decrease sepsis and serious infection (by only 3 - 4%), with no mortality benefit.[39,40] In limited resource settings, such as the SA public sector, these small benefits are insufficient to justify routine use.

Conclusions
Immunoglobulin therapy is an expensive and complex therapy that can be lifesaving. To ensure that SA patients access therapy appropriately, clinicians must be well informed on the available evidence base to motivate successfully. As many of these conditions are uncommon, clinicians who do not regularly prescribe immunoglobulins need to be aware of important product and patient factors guiding safe and effective use. It is hoped that this article serves as an effective interim measure during the ongoing development of formal SA immunoglobulin therapy guidelines to improve and advocate access and appropriate use.

References