Review article

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Intravenous immunoglobulins in dermatology. Part 1: biological mechanisms and methods of administration

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Summary

Intravenous immunoglobulin (IVIg) is a solution of human IgG, salt, sugars and solvents, which is used to treat a multitude of diseases. Although IVIg has been known to treat many diseases safely and successfully, there are relatively few supporting randomized controlled trials. In this article, we review the biological mechanisms of IVIg in dermatological disorders and the practicalities of its use, including its mechanism of action, dosing, availability, costs and adverse effects.

Introduction

IVIg is comprised of human plasma-derived IgG along with sugars, salts and solvents.[1] It is created from a combination of blood donors and plasma pools, and has been used in clinical practice for over 50 years.[2] Using thousands of plasma pools generates a risk of pathogen transmission to the recipient.[3] Fractionation, chromatography, virus inactivation and removal are the combined steps used today (in conjunction with donor screening) to decontaminate IVIg of infective diseases, including human immunodeficiency virus, hepatitis, prions and smaller encapsulated viruses.[2] Currently, the process of fractionation uses polyethylene glycol, which enables separation of IgG from plasma, which is then reprecipitated several times in conjunction with ethanol in order to create a clean product.[2] Solvents and detergents are then used to further inactivate any residual viruses, in combination with nanofiltration to eliminate prions.[4]

There are multiple diseases for which IVIg is of clinical utility; these are listed in the NHS Clinical Guidelines for Immunoglobulin Use[5] and discussed in detail in our accompanying part 2 review.

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Mechanism of action

The mechanism of action of IVIg remains largely unknown, but hypotheses include IVIg-mediated Fc receptor blockade, complement inhibition, dendritic cell downregulation and enhancement of sensitivity to corticosteroids.[2] Postulated modes of action include inhibitory effect upon T-cell function, creation of antibodies against subclasses of T lymphocytes (including CD4 and human leucocyte antigen), B-lymphocyte apoptosis, inhibition of phagocytotic processes, blockade of dendritic cell maturation and thus interleukin-2 activation, and complement inhibition via inactivating C3 precursors[6] (summarized in Table 1).

Dosing, availability and costs of intravenous immunoglobulin therapy

IVIg is licensed as 5% or 10% IgG solutions. Depending upon the manufacturer, some IVIg products are lyophilized liquid and others are ready to use formulations that do not require dilution. Lyophilized IVIg is less costly initially; however, as it requires reconstitution and more nursing input/bed occupancy due to requirement of slower infusion times compared with ready to use solutions, it works out more expensive. It has been estimated that lyophilized IVIg is ultimately €59.42/patient/infusion more expensive than ready-to-use solutions, and has a higher adverse effect (AE) profile.[7] Importantly, the various manufactured

Table 1 Mechanisms of action of intravenous immunoglobulin.

Stimulation and induction of FcγR IIB expression
Blocking of FcR
'Masking of autoantigens
Neutralization of molecules with cytochemical activities (IL-1, IL-6, IL-10, TNF-α)
Formation of immunocomplexes
Elimination of autoantigens
Binding of superantigens and TCR
Binding of HLA-I molecules
Interference with cytotoxic T lymphocytes
Apoptosis induction
Binding and activation of FAS
Binding of B clones antigen CD5
Blocking of autoantibody synthesis
Increase of production of soluble receptors and cytokine receptor antagonists (sTNF, IL-1Ra)
Inhibition of adhesion molecules (LFA-1, ICAM-1, ELAM-1)
Strengthening of T suppressor action
Interference with opsonization and cell lysis processes mediated by C3b, C3a and C5a
Inhibition of MMP-9 synthesis by macrophages
Inhibition of cytokine synthesis (IL-2, IL-4, IL-6, IL-10, TNF-α, TNF-β, IFN-γ)
Fab + Fc binding to FcγR on B lymphocytes
Reduction of autoantibody synthesis
Neutralization of autoantibodies
Increase of catabolism of autoantibodies (IgG)
Increase of FcRn saturation

ELAM, endothelial–leukocyte adhesion molecule; FcγR, Fcγ receptor; FcRn, neonatal Fc receptor; HLA, human leucocyte; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1Ra, IL-1 receptor antagonis; LFA, lymphocyte function-associated antigen; MMP, matrix metalloproteinase; TCR, T-cell receptor; sTNF, soluble tumour necrosis factor; TNF, tumour necrosis factor.

products are not interchangeable, and AE profile, administration rate and tolerability vary between brands, hence it is paramount that the clinician and pharmacist are aware of the benefits and drawbacks of the various brands.[8] IVIg formulations vary with respect to Food and Drug Administeation approval indication, half-life, storage requirements, contra-indications (such as hyperprolinaemia with PrIVIgen 10%) and administration.[9]

Common IVIg 10% brands include PrIVIgen 10% (CSL Behring, King of Prussia, PA, USA), Flebogamma DIF 10%, Gamunex 10% and Gamunex-C (all Grifols, Barcelona, Spain), Gammaked (Kedrion Biopharma, Fort Lee, NJ, USA), BIVIgAM NF (Biotest Pharmaceuticals Corp., Boca Raton, FL, USA), Octagam 10% (Octopharma, Charlotte, NC, USA) and Gammagard liquid (Baxter HealthCare Corp., Deerfield, IL, USA).[10] Common IVIg 5% and lyophilized brands include Gammaplex (Bio Products Laboratory, Durham, NC, USA), Flebogamma DIF 5% (Grifols), Octagam 5% (Octapharma), Carimue NF (CSL Behring) and Gammagard S/D (Baxter Healthcare Corp.).[11] BDI Pharma (Columbia, SC, USA) provides detailed tables for the above with full breakdown of each product's contraindications, IgA content, half-life, administration route and available sizes so that clinicians and pharmacists can select the most suitable product for each individual patient, according to their disease profile, comorbidities and risk profile. The same formulation should be used in a single patient receiving repeated treatments.

Dosage is dependent on body weight. The clinical guidelines for immunoglobulin use advise that the standard dose for IVIg is 2 g/kg divided into five once-daily infusions of 0.4 g/kg; however, clinicians commonly use two daily doses of 1 g/kg, which is acceptable.[5] Currently, the above doses are based on actual body weight; however, there is ongoing research into the use of ideal body weight (IBW) dosing of IVIg. Currently, IBW dosing is only recommended if BMI is > 30 or if actual weight is $> 20\%$ higher than IBW.

There are strict criteria for the indications of immunoglobulin use applying to both short- and long-term courses, with supporting evidence summarized in the NHS guidelines.[5] In most conditions, IVIg does not form the first-line therapy, with the exception of Kawasaki disease. Furthermore, the efficacy of IVIg is still unclear, and efficacy outcomes are currently being monitored for the majority of indications, requiring hospital trusts to record IVIg cases on their databases in order to get funding.[5] An example of typical costing for IVIg for a four-cycle course for a 70-kg person at 2 g/kg costs around £17 500,[12] compared with $26 000 in the USA.[12]

Adverse effects

Adverse effects (AEs) affect $< 5\%$ of patients treated with IVIg,[13] and occur more frequently in patients who are IVIg-naive or at risk of bacterial infection.[2] IgA-deficient individuals produce anti-IgA antibodies that implement the severe reaction, hence part of the purification process of chromatography has the aim of IgA removal to prevent infusion-related anaphylactic reaction.[2] Immediate reactions (during the first hour of the infusion) include headache, nausea, fever, chills, autonomic changes (such as blood pressure change and tachycardia), malaise, myalgia, arthralgia, chest discomfort, skin reaction, fatigue, dyspnoea, back pain, vomiting and diarrhoea. Delayed reactions include headaches, aseptic meningitis, acute renal failure,[18] thromboembolic events,

haematological complications, pulmonary complications and pseudohyponatremia.

Haemolytic reactions, although rare, can be severe, and therefore IVIg has to be compatible with a certain level of ABO blood group antibodies in order to reduce the incidence of severe haemolysis. High doses of IVIg (2 g/kg) and blood types A, B or AB increase the risk of post-IVIg anaemia.[14]

Milder AEs include nausea, fever, tachycardia, facial flushing and lower back pain (similar to blood transfusion reactions) and can be reduced by intravenous hydrocortisone and/or chlorphenamine and slowing of the transfusion rate.[2] Baseline blood tests should be performed prior to treatment, including full blood count, renal function, liver function and blood-borne virus screening.[6]

More serious AEs include transient ischaemic attack, stroke, myocardial infarction, pulmonary embolus, Stevens–Johnson syndrome (SJS), acute renal failure, aseptic meningitis and cardiac arrest.[2] The risk of an arterial thrombosis post-IVIg is quadruple that of a venous thrombosis,[15] and is more likely to be associated with atherosclerotic disease and a shorter time period post-treatment. whereas venous thrombosis is associated with obesity, immobility and a longer time period post-treatment. One article collated 65 cases of thrombosis post-IVIg over a 34-year time span, and found that the incidence of IVIg-associated thrombosis ranged between 0.15% and 1.2% per treatment.[15] Mechanisms of thrombosis include hypercoagulability secondary to increased blood viscosity, and effects on the clotting cascade, leading to raised fibrinogen and platelet activity. High-risk patients, including those with advanced age, hypertension or coronary artery disease, should be screened appropriately for underlying thrombosis, and prophylactic anticoagulation should be considered.[15,16]

One study found an incidence of 11% (n = 54) for aseptic meningitis within 24 h of IVIg infusion, with a higher risk of development in patients with a previous history of migraine or those on high-dose IVIg regimens, although the mechanism of this is not fully understood.[17]

Acute kidney injury has been reported following treatment, and this tends to resolve following cessation of therapy, attributed to the reversible effect immunoglobulins have on glomerular and tubular cell function.

Conclusion

This review provides the background knowledge required by clinicians intending to use IVIg. Our accompanying review elaborates on the indications for and outcomes following IVIg use in the full range of cutaneous conditions.

Learning points

- IVIg is made up predominantly of human IgG, salt and sugar, and requires monitoring during infusion.
- The mechanism of action of IVIg is is multifactorial and complex.
- The AEs of IVIg can be serious, and include transient ischaemic attack, stroke, myocardial infarction, pulmonary embolism, SJS, acute renal failure, aseptic meningitis and cardiac arrest.
- This review enables clinicians to understand the basic concepts behind IVIg to enable them to evaluate the latest evidence using up-to-date guidelines in order to decide when to use IVIg as a therapeutic treatment.
- The review provides concise information on the mechanism of action of IVIg.
- Dosing, availability and costs of IVIg are discussed.

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CPD questions

Learning objective

To demonstrate up-to-date knowledge in the clinicial indications and outcomes of intravenous immunoglobulin therapy.

Question 1

Which immunoglobulin is the main constituent of immunoglobulin (IVIg)?
(a) IgA.
(b) IgE.
(c) IgG.
(d) IgM.
(e) IgD.

Question 2

Which immunoglobulin should be checked prior to infusion with intravenous immunoglobulin (IVIg) to avoid anaphylaxis?
(a) IgA.
(b) IgE.
(c) IgG.
(d) IgM.
(e) IgD.

Question 3

Which of the following parameters determines the dose of intravenous immunoglobulin (IVIg) to be administered for a given indication?
(a) Age.
(b) Body surface area.
(c) Body weight.
(d) Disease severity.
(e) Estimated glomerular filtration rate.

Question 4

Which of the following mechanisms of intravenous immunoglobulin (IVIg) is incorrect?
(a) Complement inhibition.
(b) Interleukin-2 activation.
(c) Induction of apoptosis.
(d) Upregulation of dendritic cells.
(e) Fas binding and activation.

Question 5

Adverse effects of intravenous immunoglobulin (IVIg) include which of the following?
(a) Stroke.
(b) Myocardial infarction.
(c) Acute renal failure.
(d) Aseptic meningitis.
(e) All of the above.

Instructions for answering questions

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- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
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