Intravenous Immunoglobulin in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of Intravenous Immunoglobulin (IVIg) when used in the management of irAEs caused by immune-checkpoint inhibitors.

It should be noted that this use may be off-label; relevant governance processes within each organisation should be followed to ensure the risks associated with this are mitigated

British Oncology Pharmacy Association in Collaboration with The Immuno-Oncology Clinical Network

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Contents

1. Introduction

- Immunoglobulin therapy is a blood-based treatment. Immunoglobulin is made from plasma separated out from donated blood. During manufacture everything except a type of immunoglobulin called immunoglobulin G (IgG) is removed from the plasma. IV immunoglobulin G, known as IVIg is licenced for replacement therapy and immunomodulation treatment for conditions including primary immune thrombocytopenia and Guillain Barré syndrome. Its use for irAEs is as an immunomodulator.

- ASCO guidance on the management of irAEs highlights potential IVIg use in haematological irAEs, dermatological irAEs, pneumonitis, myositis, myasthenia gravis, Guillain–Barré syndrome, encephalitis, demyelinating disease, and uveitis. These recommendations are largely based on case reports using IVIg in wide array of checkpoint inhibitor associated toxicities.

- There is evidence for use of IVIg in patients as an immunomodulator for several immune mediated conditions as outlined by the Department of Health and NHS England Clinical Commissioning Policy.

- Due to national shortages, any use of IVIg in England for the treatment of immune checkpoint inhibitor toxicity must fall within the existing NHSE clinical commissioning policy for use within the NHS.

- Sub-Regional Immunoglobulin Assessment Panels (SRIAP) review and approve the use of immunoglobulin in all patients. Depending on the indication, these may require prior or retrospective approvals and every gram of IVIG used must be accounted for on the national IVIg database. In Scotland, Wales and Northern Ireland, local commissioning processes should be followed to access IVIg on the NHS.

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate IVIg in adult patients. It is not a clinical guideline, but a consensus view of current use of IVIg when used for irAEs. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Hypersensitivity to IVIg.
- Hypersensitivity to any of the excipients.
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.
- Patients with hyperprolinaemia type I or II.

2.2 Precautions

- **Infusion reactions:** Ensure that the infusion is started at the appropriate rate and titrated depending on tolerance according to the monitoring (detailed below). This is particularly important if it is a patient's first IVIg infusion, if they have changed IVIg product or if there has been a long interval since any previous IVIg administration (> 8 weeks).

- **Active infection:** The rate of infusion reactions may be increased in patients with active infection.
- **Immunisations:** IVIg may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella for a period of at least 6 weeks and up to 3 months. After administration of IVIg, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Patients receiving measles vaccine should have their antibody status checked.
- **Arterial or venous thromboembolic disease:** Increased risk of these events due to a relative increase in blood viscosity. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilia disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).
- **Acute renal failure:** Risk factors include pre-existing renal insufficiency, diabetes mellitus, hypovolemia, being overweight, concomitant nephrotoxic medicinal products, age over 65 or products containing sucrose as a stabiliser. Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals.
- **Interference with serological testing:** Rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red blood cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test). IVIG can also cause false positives for other infectious diseases such as hepatitis and syphilis.
- **Haemolysis:** IVIg contains anti-A and anti-B antibodies; non-O blood group patients may develop haemolysis, especially if given high dose IVIg.
- **Risk of aseptic meningitis:** This has been reported with IVIG treatment (higher risk with the higher dose of 2g/Kg). It usually occurs within several hours to 2 days post infusion. Cerebrospinal fluid (CSF studies are frequently positive with pleocytosis up to several thousand cells per mm^3 (predominantly granulocyte series) and elevated protein levels up to several hundred mg/dL. Other causes of meningitis should be ruled out.
- **Transfusion-related acute lung injury (TRALI):** There have been some reports of acute non-cardiogenic pulmonary oedema. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for this and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.
- **Transmissible agents:** The possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens including the prions responsible for variant CJD.
- **Look carefully at the individual IVIg monographs** some products must be avoided in hereditary fructose intolerance due to their sorbitol content. Also, IVIg products containing maltose, icodextrin, galactose and xylose can be misinterpreted as glucose and result in erroneously elevated serum glucose levels on tests.
- **Traceability:** As a blood product the name and the batch number of the administered product should be clearly recorded. This information also needs to be recorded in the national database.

2.3 Pregnancy advice

IVIg has been shown to cross the placenta and its use is cautioned in pregnancy and breast feeding by the manufacturer as the safety in this group has not been tested in clinical trials. However available evidence does not indicate any adverse effects on the course of pregnancy, foetus or the neonate.

2.4 Pre-treatment assessment

- Baseline height and weight (to calculate adjusted ideal body weight)
- Baseline FBC, U+Es, LFTs.
- Ensure the patient is well hydrated and good urine output e.g 1ml/mk/hr. May require pre-hydration fluids.
- Baseline temperature, pulse, respiratory rate, oxygen saturations and blood pressure.
- Baseline virology: Hepatitis B Core Antibody, Hepatitis C, HIV and request the sample to be stored. This is in case of concern over virus transmission at a later date.
- ABO blood group (IVIg contains anti-A and anti-B antibodies; non-O blood group patients treated with IVIg may develop haemolysis, especially if given high dose IVIg)
- Indication specific baseline tests as outlined in the commissioning criteria for each indication.

2.5 Pharmaceutical form

Solution for infusion.

Brands may vary according to local supply arrangements. Specific characteristics will vary with product used.

2.6 Dosage

Dose and regimen are dependent on the individual indication (see product SPC or NHS clinical commissioning policy). Dosage may vary from 1-2g/kg over 1-5 days depending on the indication. It is advised to divide the infusion of high doses (greater than 1g/kg) over more than 1 day.

- The dose of immunoglobulin should be based on the adjusted ideal body weight for obese patients (BMI > 30kg/m^2).
- The dose administered should be rounded down to the nearest whole vial.
- Where the dose is split over multiple days to the nearest whole vial, the daily dose may differ.

For example:

Calculation of IBW (male)	IBW = 50 + (0.91 x [Height(cm) – 152.4]) = 50 + (0.91 x [170-152.4]) = 66kg
Calculation of total dose	2 x 66kg = 132g → rounded down to nearest 5g vial = 130g
Split total dose over 5 days	• Day 1: 30g • Day 2: 20g • Day 3: 30g • Day 4: 20g • Day 5: 30g

- Ideal body weight formula:

-Men: Ideal body weight (IBW) = 50 kg + (0.91 x (height in cm – 152.4))
-Women: Ideal body weight (IBW) = 45.5 kg + (0.91 x (height in cm – 152.4))

IVIg Dose Calculator with BMI and Speciality Recommendations (transfusionontario.org)

2.7 Method of administration

General advice

- IVIg should be administered in a controlled healthcare setting so that emergency treatment (for anaphylaxis) can be administered immediately where necessary.
- Remove from the fridge at least 30 minutes prior to administration. Ensure the product is at room temperature
- Dilution: IVIg Should be administered undiluted as an IV infusion from its container.
- Route: May be administered via central or peripheral route. Administer using an infusion pump.
- Compatibility: It should be infused via a separate line and should not be mixed with other IV fluids or medications.
- Extravasation: May cause tissue damage due to low pH. No evidence for specific antidote; elevate limb and provide analgesia. Refer to local extravasation guidance.
- Traceability: Batch numbers should be recorded to ensure traceability of the blood product.

Pre-medications

- May be considered as primary prophylaxis, or secondary prophylaxis following a prior infusion reaction.
- Primary prophylactic medications may be included at clinical discretion.

  -Chlorphenamine 10mg IV/4mg PO or Cetirizine 10mg PO
  -Hydrocortisone 100mg IV
  -Paracetamol 1g PO/IV (if not already administered within 4 hours, if below 50kg dose 15mg/kg)

- When required medications should always be prescribed in advance (in case of reaction):

  -Chlorphenamine 10mg IV
  -Paracetamol 1g IV (if not already administered within 4 hours, if below 50kg dose 15mg/kg)
  -Hydrocortisone 100mg IV
  -Salbutamol 2.5-5mg NEB

If a patient has a reaction to IVIg then halt the infusion and restart at the last tolerated rate. Ensure that the correct infusion rate titration has been followed.

Anaphylaxis

In the event of severe infusion reactions or anaphylaxis this should be managed urgently as per local protocol.

UK SACT Board Guidance on Anaphylaxis and hypersensitivity reactions: guidance for the management of adults receiving intravenous systemic anti-cancer therapy (SACT) for the treatment of solid tumours

Infusion rate

The recommended infusion starting rate is variable depending on IVIg product.

Consult SPC or Medusa Injectable medicines guide (provides the recommended infusion rates in addition to example infusion tables for weight ranges).

Stepwise titration of the infusion rate should be followed for each subsequent infusion per the manufacturers guidance. Once the maximum rate that a patient can tolerate in known this should be documented in their clinical record for future reference.

If patient deemed to be at risk of fluid overload consider administering at a slower rate or splitting the infusion over multiple days. If administered before, confirm the maximum rate tolerated.

Monitoring during IVIg Infusion

- Monitoring: temperature, pulse, respiratory rate, oxygen saturations and blood pressure.
- Symptoms: headache, chills, myalgia, wheezing/dyspnoea, back pain, nausea/vomiting, rash, itching.

Timing of monitoring

1st Infusion	Subsequent Infusions
Prior to start of infusion	Prior to start of infusion
15 minutes after starting, then every 30 minutes (or after any rate increase) until infusion is completed	End of treatment
Observe for 1 hour after the infusion is completed	Observe for 20 minutes after the infusion is completed

In the event of an infusion reaction please consult the following guidance for assessment of symptoms.

UK SACT Board Guidance on Anaphylaxis and hypersensitivity reactions: guidance for the management of adults receiving intravenous systemic anti-cancer therapy (SACT) for the treatment of solid tumours

2.8 Is there therapeutic Drug Monitoring?

No therapeutic drug monitoring is required.

2.9 Other monitoring

Depending on the indication for IVIg there may need to be additional information collected both at baseline and following IVIg treatment. These are outlined in the IVIg commissioning guidance.

Monitoring during and following the infusion is outlined above.

2.10 Adverse effects

- The table below outlines the broad range of adverse events that patients can experience with IVIG.
- This is not an exhaustive list. See SmPC for further details.

System	Adverse Effects
Blood and lymphatic system disorders	Haemolysis (mild), Neutropenia/Leukopenia, Haemolytic anaemia
Immune system disorders	Infusion related reaction, Hypersensitivity
Nervous system disorders	Headache, Dysgeusia, Sensory disturbance, Aseptic meningitis syndrome (AMS)
Vascular disorders	Hypertension, Thrombophlebitis superficial, Hyperaemia
Gastrointestinal disorders	Nausea, Vomiting, Gastrointestinal pain, Diarrhoea
Skin and subcutaneous tissue disorders	Maculo-papular rash, Pruritus, Erythema

Musculoskeletal and connective tissue disorders	Arthralgia, Back pain, Bone pain, Myalgia
Respiratory disorders	Transfusion-related acute lung injury (TRALI)
General disorders and administration site conditions	Pyrexia, Chills, Feeling hot, Discomfort
Investigations	Body temperature increased, Coombs test (indirect and direct) positive

2.11 Drug interactions

The table below lists the most common interactions but is not exhaustive. The SmPC and other drug interactions resources should be further consulted.

Drug	Interaction
Live attenuated virus vaccines	May impair response to live attenuated vaccines for up to 3 months. Patients receiving measles vaccine up to one year after IVIg should have antibody levels checked.
Loop diuretics	Avoidance of concomitant use where possible, increased renal toxicity.

Test	Interaction
Serological assays	False positive results may occur, in particular direct antiglobulin test
Blood Glucose Monitoring systems	If maltose in IVIg is measured as glucose, this may result in falsely high glucose levels. Check with glucose monitoring equipment information or manufacturer.

2.12 Advice to patients

Intravenous Immunoglobulin (IVIg) will be administered by an intravenous infusion (drip) in a hospital setting. This will usually be over between 1 and 5 days.

You will be monitored closely while having the infusion. If you feel unwell during or after the infusion has finished, please contact your healthcare provider where you received the infusion. Some side effects may occur after the infusion has taken place.

If receiving any live vaccines up to 1 year following the IVIg infusion, you must let your healthcare team know that you have received this treatment as IVIg may make vaccinations less effective

3. Appendix 1 Intravenous Immunoglobulin Patient Information Leaflet

What is Intravenous Immunoglobulin (IVIg)?

Intravenous Immunoglobulin (IVIg) is made from donated blood-derived plasma. During manufacture, everything except a type of immunoglobulin called immunoglobulin G (IgG) is removed from the plasma and this then makes IVIg. It is used for a number of different conditions where the immune system has become overactive and is causing problems in the body.

It has also been found to be useful for some of the side-effects that can occur when patients are given immunotherapy to treat cancer. In this case the immune system has become active against one part of the body and may be causing damage; IVIg can dampen down this response.

The dose is worked out based on your body weight. There are lots of different brands of IVIg.

How do I take is IVIg?

IVIg will be administered via an intravenous infusion (drip) in the hospital. This is usually over several hours each day for between 1 and 5 days for each course.

How long will I need to have IVIg?

Some patients may require only a single course of IVIg while others may require repeated courses. This will be determined by what immune related side effect you have and how much the IVIg is helping with this.

Does IVIg have any side-effects?

There are several possible side effects that you may notice, although many people do not experience any of these. Side effects may include headache, chills, stomach pain, fever, sickness, back pain and tiredness.

You may notice a rash, raised temperature, shivering, or itching while receiving the infusion. This can generally be managed by reducing the speed of the infusion (drip) or stopping the drip. Medications may be given to help control these symptoms.

Very rarely, people have a severe allergic reaction to the treatment that can cause chest tightness, skin rash, breathing difficulties, swelling of the face or tongue and a drop in blood pressure. Medical and nursing staff will be monitoring you for any of these symptoms and will be able to treat you accordingly.

IVIg can affect how well your kidneys are working. This will be checked before the infusion. Try to make sure you drink plenty of fluids before your infusions.

Other very rare complications of treatment can include inflammation around the brain, anaemia, increased clotting of the blood (causing deep venous thrombosis, heart attack or stroke).

<u>Contact your team if you develop any of the symptoms either during or after your infusion:</u>

- Severe headache, eye pain, extreme drowsiness
- Facial and/or tongue swelling
- Difficulty breathing, chest tightness
- Changes in urine colour (red urine, dark coloured urine)
- Intense back pain that is new
- Feeling faint or severe fatigue

As immunoglobulins are blood products, they are screened to ensure they do not contain viruses such as Hepatitis B, Hepatitis C and HIV. It is possible, but very unlikely, that there are viruses and other proteins that could be passed on which we do not currently know about and therefore cannot test for. If you have any concerns after treatment, you should consult your doctor for further advice.

If you would normally drive, we advise that you arrange for someone to collect you, at least following the first few treatments.

Can I still be vaccinated?

IVIg may affect your response to live attenuated vaccines for up to 3 months.

If you receive a measles vaccine up to one year after IVIg infusion, then antibody levels may need to be checked to ensure it has worked. Please ask your healthcare team for further information if required.

Is it safe to become pregnant while I am receiving IVIg?

You may have already had these conversations with your oncology team before starting immunotherapy. Please highlight to your team if you believe you may be pregnant.

In the case of IVIg based on clinical experience, it is not thought to have negative effects on the course of pregnancy, towards the foetus or neonate although there is limited information in this situation.

Can I take other medicines whilst I am receiving IVIg?

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter.

Supply of IVIg.

It will be prescribed and administered in the hospital.

Who can I contact for further information?

If you have any queries about your IVIg, the best people to speak to are the oncology team who you are under, the team of specialists who have prescribed the IVIg for you, or an oncology pharmacist.

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6. Document control

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