Organising an IVIg (Intragram) infusion

Request and ordering

IVIg comprises of gamma globulins derived from purified pooled plasma of thousands of donors, consisting mainly of polyspecific IgG. It has pleotropic immunomodulatory and anti-inflammatory actions, and although not fully delineated, the proposed mechanisms include inhibition of innate and adaptive immune cell activation and synthesis of inflammatory mediators, and induction of anti-inflammatory cells and molecules[(2)].

Indications for IVIg use in the setting of solid organ transplantation is directed by the **National Blood Authority's (NBA)** National Immunoglobulin Governance Program, and must be adhered to by everyone involved in the prescription, ordering, dispensing, supply and management of immunoglobulin product (https://www.blood.gov.au/Ig).

IVIg products available in Australia:

- Australian produced:
    - Privigen® AU (nb: INTRAGAM 10 being phased out in 2023)
- Imported:
    - Fleboamma® 5%
    - Flebogamma® 10%

The NBA determines which patient conditions qualify for funded Australian or imported products.

Contraindications

- True anaphylactic reactions to human immunoglobulins (especially in patients with antibodies against IgA)
- Privigen and Flebogamma are contraindicated in IgA deficient patients with anti-IgA antibodies
- Flebogamma is contraindicated in patients with hereditary problem of fructose intolerance and should not be administered to children under two years of age as this may be undiagnosed.

Criteria and dosing for use in the setting of solid organ transplantation

Updates on the criteria for use are available through
https://www.criteria.blood.gov.au/MedicalCondition/View/2484

At the time of writing of this document, the indications for use are:

- Immediate pre and/or post-transplant where donor specific antibody(s)* prevent transplantation or threaten transplantation (**this includes blood group, HLA and/or non-HLA antibodies)*
- Initial treatment of acute antibody mediated transplant rejection
- Treatment of ongoing active antibody mediated transplant rejection
- Ongoing desensitisation of patients to improve the likelihood of transplantation
- Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. The dose of Ig product is calculated based on a patient's weight. Dose will vary, depending on whether Ig treatment has been prescribed as a replacement therapy or immunomodulation therapy.

Medical officers may adjust the dose for ideal body weight. This is facilitated within BloodSTAR through an algorithmic calculator https://www.blood.gov.au/bloodstar-calculator-adjusting-ig-dose-

ideal-body-weight. Adjusting dose for ideal body weight is not recommended in patients aged less than 18 years, who are less than 152cm in height, or who are pregnant. Furthermore, if the BloodSTAR calculator is applied but the actual weight of the patient is less than the dose determined weight, the Ig dose should be calculated using the patient's actual weight.

Indications and Dose recommendations of IVIG in Kidney Transplantation (as outlined by the National Blood Authority)

Indication	**Dose recommendations***
Immediate pre and/or post-transplant where donor specific antibody(s) prevent transplantation or threaten transplantation	• **Single dose (IVIg)** - Up to 2 g/kg to a maximum of 140g as a single dose.* • **Repeated Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in separate doses up to a total maximum dose of 2g/Kg/8-week period.
Initial treatment of acute antibody mediated transplant rejection	• **Single Dose (IVIg)** - Up to 2 g/kg to a maximum of 140 g as a single dose.* • **Recurrent Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/8 week period.
Treatment of ongoing active antibody mediated transplant rejection	• **IVIg with plasma exchange (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/4 week period.
Ongoing desensitisation of patients to improve the likelihood of transplantation	• **Maintenance Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/4 week period.
Treatment or prevention of graft rejection where the use of conventional immunosuppressive therapies is contraindicated or poses a threat to the graft or patient	• **Recurrent Dose (IVIg)** - 0.1 to 0.5 g/kg which may be given in divided doses up to a total of 2g/Kg in a 4 week period. • **Single divided dose (IVIg)** - Up to 2 g/kg as a single dose.*

*Where 2g/kg is administered as a single dose, we advise pre-hydration with 500mL to 1L of normal saline and a single therapeutic dose of low molecular weight heparin prior to IVIG administration, and slow infusion rate, which may reduce thrombosis risk.

Side effects

Side effects are usually mild and transient which usually occur soon after the infusion. These include headaches, flushing, fever, chills, fatigue, nausea, diarrhoea, blood pressure changes and

tachycardia. These tend to usually occur with the first infusion, and may respond to slowing the infusion rate.
More serious adverse reactions such as acute renal failure, thrombotic events- both venous and arterial including AVF thromboses, aseptic meningitis, hematologic complications and anaphylactic reaction are extremely rare[3]. Thrombotic complications may have a greater association with high dose IVIg administration (ie 2g/kg in one infusion). This is not a dose routinely used in our transplant service.

Administration of IVIG

This is usually administered in the outpatient clinic (eg renal clinic or ambulatory care unit). Written Consent is needed as it is a blood product, the indication and side effects/risks need to be discussed with the patient prior. Administration should follow the local hospital protocol for IVIg administration, **except where high dose (2g/kg in a single dose) is being administered, pre-hydration with 500mL - 1L of normal saline along with a single therapeutic dose of low molecular weight heparin should be administered prior to the infusion, and a slow infusion rate, may reduce thrombosis risk[4,5].**

Seeking authorisation/approval

The Australian Red Cross Lifeblood (Lifeblood) is contracted by the National Blood Authority (NBA) as the authoriser and distributor of all IVIg funded under the national blood supply arrangements. In seeking authorisation, the requesting medical officer will be asked to provide information to Lifeblood through www.blood.gov.au/bloodstar to establish that the request meets the Criteria.

Once approval is granted, it is only provided for the duration stipulated in the approval document and is in line with what is outlined in the above section on Criteria and dosing. Even if the requested amount of IVIg has not been completely used/dispensed, repeat approval will be needed if the period of approval has lapsed.

References

1. National Blood Authority online resource for IVIG, last accessed August 1st 2021 https://www.blood.gov.au/Intravenous-Ig
2. Galeotti C, Kaveri SV, Bayry J. Molecular and immunological biomarkers to predict IVIg response. Trends Mol Med. 2015;21(3):145–7. pmid:2568069
3. Guo et al. Adverse Effects of Immunoglobulin Therapy. Front Immuno. 2018 9: 1299.
4. Vo AA et al. Safety and adverse event profiles of intravenous gammaglobulin products used for immunomodulation: a single centre experience. Clin J Am Soc Nephrol. 2006 Jul; 1(4): 844-52.
5. Huang L, Kanellis J, Mulley W. Slow and steady. Reducing thrombotic events in renal transplant recipients treated with IVIg for antibody-mediated rejection.

Urgent Infusion

- For urgent same day infusion contact Red Cross 1300 478 348
- Inform St George Hospital blood bank the request has been sent to the Red Cross

Reviewed May 2023 Tania Burns/Karen Keung