Position Statement Subcutaneous Immunoglobulin (SCIg)

The purpose of this document is to provide the recommendations of the Australasian Society of Clinical Immunology and Allergy (ASCIA) regarding subcutaneous immunoglobulin (SCIg) replacement therapy in Australia and New Zealand.

SUMMARY OF RECOMMENDATIONS

1. Immunoglobulin replacement therapy (IRT) is the standard of care for patients with antibody deficiency due to a primary immune deficiency (PID) disease or secondary immune deficiency. IRT should be readily available to these patients while under the active care of a specialist immunology and allergy physician (PID or secondary immune deficiency) or other specialist physician (secondary immune deficiency).
2. Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) replacement therapy comprise standard of care treatment and should be available for patients in Australia and New Zealand with antibody deficiency due to a primary immune deficiency (PID) disease or secondary immune deficiency.
3. The choice of route (IVIg or SCIg) for immunoglobulin replacement therapy (IRT) will depend on several factors, including patient characteristics, clinical indication, venous access, side effects, rural or remote location, treatment plan compliance and patient choice.
4. SCIg infusions for immunoglobulin replacement therapy (IRT) are efficacious, well tolerated, have a favourable safety profile and should be available to all patients where clinically appropriate, with relevant education and follow up care.

KEYWORDS:

Immunoglobulin (Ig)

Immunoglobulin G (IgG)

Immunoglobulin replacement therapy (IRT)

Intravenous immunoglobulin (IVIg)

Primary immune deficiency (PID) disease

Quality of life (QOL)

Secondary immune deficiency

Subcutaneous immunoglobulin (SCIg)

RECOMMENDATION 1:

Immunoglobulin replacement therapy (IRT) is the standard of care for patients with antibody deficiency due to a primary immune deficiency (PID) disease or secondary immune deficiency. IRT should be readily available to these patients while under the active care of a specialist immunology and allergy physician (PID or secondary immune deficiency) or other specialist physician (secondary immune deficiency).

PID diseases and secondary immune deficiencies predispose patients to recurrent infections and long term organ damage from chronic infections.

One of the most important, effective and commonly used treatments for PID diseases is IRT, to replace immunoglobulins (antibodies) that are insufficient in these patients[1,2,3]. IRT is usually required lifelong to prevent or alleviate infections and this therapy can be life saving[4].

Access to IRT is guided by clear prescribing criteria to ensure clinically appropriate and economical use of immunoglobulin products.

IRT can be administered by:

- Injecting into the vein (intravenous immunoglobulin or IVIg), usually monthly in hospital; or
- Injecting under the skin (subcutaneous immunoglobulin or SCIg), usually 1-3 times per week, which can be given at home by the patient or carer.

RECOMMENDATION 2:

Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) replacement therapy comprise standard of care treatment and should be available for patients in Australia and New Zealand with antibody deficiency due to a primary immune deficiency (PID) disease or secondary immune deficiency.

The introduction of IRT has greatly improved health related quality of life (QOL) for patients with PID diseases[5].

Both IVIg and SCIg replacement therapy:

- Offer protection from serious bacterial infections[6].
- Have been shown to have good safety profiles[6].

RECOMMENDATION 3:

The choice of route (IVIg or SCIg) for immunoglobulin replacement therapy (IRT) will depend on several factors, including patient characteristics, clinical indication, venous access, side effects, rural or remote location, treatment plan compliance and patient choice.

Various factors influence the decision as to whether IVIg or SCIg replacement therapy is the best option for a given patient, including availability of immunoglobulin delivery systems, appropriate products, patient factors, logistic considerations, patient preference and cost[7].

There are advantages and disadvantages for both IVIg and SCIg therapy (outlined in Table 1) and the preferred route may vary at different times during a given patient's life[8].

Table 1: Comparison of Pros and Cons of IVIg and SCIg therapy

	Pros	Cons
IVIg	• Less frequent infusion (monthly) • Rapid increase in serum IgG • Does not require patient training	• Usually hospital based • IV access required • Risk of immediate and systemic adverse effects • Adverse effects from high IgG levels in 12-48 hours post infusion • Symptoms related to wear off effects of IgG trough levels
SCIg	• Home based therapy • IV access not needed • Few systemic side effects • Can be used for patients with previous systemic reactions to IVIg or IV access difficulties[4,9] - SCIg therapy may be the preferred treatment in these patients • More consistent IgG levels with no wear off effects related to IgG trough levels • Improved QOL of patient and family with flexibility, independence and empowerment • Reduced hospital costs • Reduced patient travel time • Patient can take treatment with them when travelling (e.g. on holiday)	• Frequent administration (1-3 times per week) • Local side effects (swelling, induration, local inflammation, itch), which are usually transient • Some patients may require battery or spring driven pumps (although some patients may use the push method which does not require a pump) • Requires treatment plan compliance

Source: Adapted from APIIEG[8]

Other factors that may affect the choice of route for IRT (IVIg or SCIg) include:

- **Patient satisfaction –** this plays an important role in treatment decisions, particularly as patients with PID diseases require lifelong IRT[5].
- **Availability and resourcing of SCIg infusion pumps and consumables**.
- **Availability of SCIg products** - It is important that once a patient has been successfully established on a product there is ongoing supply of this product. Having a number of SCIg product options is useful for patients who have tolerability problems with one or more products.
- **Other medical conditions** - SCIg therapy may be contraindicated in some patients with severe thrombocytopenia, bleeding disorders or for patients on anticoagulation therapy and may also be problematic for patients with widespread eczema[4].
- **Less frequent infusion procedures may be preferred for some young patients**[4,10] - even though SCIg therapy has been shown to be well tolerated in infants and young children.
- **Limited subcutaneous tissue** – this may limit site options for SCIg infusions[11] although it has been successfully administered to infants.

RECOMMENDATION 4:

SCIg infusions for immunoglobulin replacement therapy (IRT) are efficacious, well tolerated, have a favourable safety profile and should be available to all patients where clinically appropriate, with relevant education and follow up care.

Studies have demonstrated that IRT using SCIg has equivalent efficacy to IVIg in preventing bacterial infections in patients with antibody deficiencies[1,5,12].

Results from a pooled analysis of seven studies of four SCIg preparations in patients with PID diseases:

- Suggest that maintaining higher steady state IgG levels results in fewer infections[13].
- Show that the incidence of infection is inversely related to the steady state IgG level and maintaining higher IgG levels are beneficial, although no given level is necessarily adequate for all patients[13].

Pharmacokinetic studies indicate that SCIg infusions result in more stable serum immunoglobulin concentrations with little fluctuation in IgG levels[5,7,9] compared to the peaks and troughs of IgG levels associated with monthly IVIg administration[14]. More stable IgG levels reduce the risk of:

- Immediate and systemic adverse effects due to high IgG levels post-infusion
- Symptoms related to wear off effects of IgG trough levels.

SCIg therapy has been shown to be well tolerated with a low risk of systemic side effects[5,10].
Whilst local tissue reactions are frequent with SCIg therapy, they are often mild and tend to improve over time[5,10]. Provision of adrenaline autoinjectors is not considered to be necessary, given the demonstrated safety of SCIg infusions.

There is a range of reasons why patients choose to undergo SCIg therapy, including:

- **Patient choice and satisfaction,** which plays an important role in treatment decisions, as patients with PID diseases require lifelong IgG therapy[5].
- **A preference for patient centred rather than institution centred treatments,** which are likely to enhance independence and self care capabilities.
- **Poor venous access or a history of severe adverse events following IVIg infusion**[9] - SCIg is universally regarded as the preparation of choice for these patients.
- **Difficulties with IVIg therapy for some patients** as the monthly infusions require repeated venous access and may result in wide variation in serum IgG[9].

SCIg can be administered by:

- Battery or spring driven pumps; or
- Push method, which does not require a pump. The push method can result in rapid infusions that are safe and well tolerated[14], however the ability to administer SCIg by the push method is dependent on patient characteristics, including strength to manually push the syringe.

Some patients who use a pump can also be trained in the push method in case there is a problem with the pump. Whilst it is widely accepted that patients should not necessarily have to pay for large expenses (e.g. pumps), the minor costs of consumables can possibly be paid for by some patients, in a similar way that applies to consumables used in other outpatient based therapy.

It is also important that restrictions for provision of SCIg do not discriminate against privately insured patients who are not treated at a public hospital.

Sufficient patient education and training at the initiation of SCIg therapy, and follow up care is essential to ensure patient safety and effective treatment delivery:

- Current operating programs suggest initial education and training (e.g. approximately 4-6 sessions) by a skilled nurse or equivalent is required for each patient commencing SCIg therapy[7,10].
- Patients and their families should be continuously supported and offered regular medical and nursing follow up care[10], for monitoring, advice and clinical assessment, equivalent to current IVIg therapy standards of delivery, which necessitate regular contact with care givers in specialist teams.

Dispensing of immunoglobulin for SCIg therapy should be set up in such a way to:

- Maximise patient convenience, with local delivery of sufficient quantity to patient's home, local pharmacy or general practitioner to last at least one month.
- Consider allowing delivery or pick up of more than one month's supply for patients who are on long term IRT and have the capacity to store product (it is important to note that some products can be unrefrigerated for specified periods).
- Ensure effective and non-wasteful usage of a limited and expensive resource.

ACKNOWLEDGEMENTS

ASCIA is the peak professional body of specialist immunology and allergy physicians in Australia and New Zealand. This document has been reviewed by ASCIA members and represents the available published literature at the time of review. The content of this document is not intended to replace professional medical advice and any questions regarding a medical diagnosis or treatment should be directed to a medical practitioner.
This document has been developed as part of the ASCIA Subcutaneous Immunoglobulin (SCIg) Project, an initiative of the Australasian Society of Clinical Immunology and Allergy (ASCIA).
The main objective of the ASCIA SCIg project is to develop documentation relating to the use of SCIg in patients with antibody deficiency due to a primary immune deficiency (PID) disease or secondary immune deficiency.
ASCIA has received unrestricted educational grants from industry (CSL Behring, Octapharma and Baxter) to assist with funding of the ASCIA SCIg Project. The content of this document, and any other ASCIA educational resources, is not influenced by industry.

Website: www.allergy.org.au
Email: projects@allergy.org.au
Postal address: PO Box 450 Balgowlah NSW Australia 2093

REFERENCES

1. Ochs HD et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol Allergy. 2006; 26 (3): 265-273.
2. Nicolay et al. Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy. Quality of Life Research. 2005; 14: 1683-1691.
3. Bonilla FA et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Annals of Allergy, Asthma & Immunology. 2005; 94: S1-S63 www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/immunodeficiency2005.pdf
4. Gaspar J GB, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Archives of Disease in Childhood 1998; 79 (1): 48-51.
5. Bezrodnik L et al. Comparative study of subcutaneous versus intravenous IgG replacement therapy in paediatric patients with primary immunodeficiency diseases: A multicentre study in Argentina. J Clin Immunol. 2013; 33: 1216-1222.
6. Lingman-Framme J, Fasth Anders. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs. 2013; 73: 1307-1319.
7. Kobrynski L. Subcutaneous immunoglobulin therapy: a new option for patients with primary immunodeficiency diseases. Biologics: Targets and Therapy. 2012; 6: 277-287.
8. Asia Pacific Immunoglobulins in Immunology Expert Group (APIIEG) Consensus Recommendations for the use of Immunoglobulin Replacement Therapy in Immune Deficiency. 2009. www.allergy.org.au/health-professionals/papers/9-papers/position-papers-guidelines/460-external-position-papers-recommendations-and-guidelines-involving-ascia-members-#s1
9. Abolhassani H et al. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: Systematic review and meta analysis. J Clin Immunol. 2012; 32: 1180-1192.
10. Gardulf, A. Immunoglobulin treatment for primary antibody deficiencies: Advantages of the subcutaneous route. Therapy Review. 2007. 105+
11. Stiehm ER, Casillas AM, Finkelstein JZ, Gallagher KT, Groncy PM, Kobayashi RH, et al. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. J Allergy Clinical Immuno. 1998; 101 (6 Pt 1): 848-9.
12. Radinsky S, Bonagura VR. Subcutaneous immunoglobulin infusion as an alternative to intravenous immunoglobulin. J Allergy Clin Immunol 2003; 112: 630-3.
13. Berger M. Incidence of infection is inversely related to steady-state (trough) serum IgG level in studies of subcutaneous IgG in PIDD. J Clin Immunol. 2011; 31 (5): 924.
14. Younger MEM, Blouin W, Duff C, Epland KB, Murphy E, Sedlak D. Nursing Guidelines for Administration of Immunoglobulin Replacement Therapy. Infusion Nurses Society. 2013; 36: 1

Content last updated July 2014