



PRIMARY IMMUNODEFICIENCIES

IMMUNOGLOBULIN REPLACEMENT THERAPY: **ONE SIZE DOESN'T FIT ALL**



ABBREVIATIONS

IG	Immunoglobulins
IPOPI	International Patient Organisation for Primary Immunodeficiencies
IV	Intravenous
PID	Primary immunodeficiency
SC	Subcutaneous

Immunoglobulin replacement therapy for primary immunodeficiencies: one size doesn't fit all (1st edition).

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INTRODUCTION

This booklet explains the variety of factors that patients with primary immunodeficiencies (PIDs) should consider, and discuss with their physician, when an immunoglobulin replacement therapy is chosen.

PIDs are a group of rare diseases that occur when components of the immune system are either not present or not working properly. There are over 280 different PIDs, varying from relatively mild conditions to diseases that are very serious and potentially life-threatening. The most common PIDs cause patients to lack proteins called immunoglobulins (IG). As IG normally help the body's immune system to recognise and neutralise infecting germs (micro-organisms such as bacteria, viruses or fungi), the lack of IG makes people susceptible to infection. IG replacement to protect against infection is, therefore, the most important therapy for these PIDs. IG can also help reduce 'autoimmune' symptoms, caused when the immune system targets part of the patient's own defence system. IG replacement therapy is a lifelong, life-saving therapy that patients must have regularly.

IG products are made from human plasma (the pale yellow liquid component of blood, donated by healthy donors) and other ingredients. As such, IG products are 'biological' medicines. IG products have been shown to be effective and they have a very good safety profile. When choosing IG replacement therapy, important factors to be considered are the dosage, and how, where and how often therapy should be given. Many different brands of IG are available, depending on where in the world you live. These differ in terms of their ingredients and how they are produced, and this can affect how patients respond to them. Therefore, the specific IG product should be chosen on an individualised basis, according to the needs and preferences of each patient — one size does not fit all! Moreover, a change of product might be appropriate for patients who do not respond well, or have troublesome side effects, while using a particular product.

If you are a patient, you should be aware of the available options and discuss with your physician which is most suitable for you. Families and carers should also be involved in these decisions. This booklet explains these factors, focusing on three important questions:

- Intravenous or subcutaneous infusion?
- Therapy in hospital or at home?
- Which formulation is best for me?

Remember, different IG products are not interchangeable or mixable. Therefore, once you are prescribed IG replacement therapy you should make sure you know exactly which product you use, so that you always receive the correct one. Any change of therapy must only be made in consultation with the prescribing physician.

IG therapy should be chosen on an individualised basis, according to your needs and preferences — one size does not fit all!

INTRAVENOUS OR SUBCUTANEOUS INFUSION?

IG is given as an infusion (or 'drip') intravenously (straight into the bloodstream through a vein) or subcutaneously (under the skin of the leg, belly or arm). Both routes are effective, and each has advantages and disadvantages, depending on your individual situation. This choice can affect whether your therapy needs to be given in a clinic or hospital, or if it can be given at home (see below).

Intravenous (IV) infusion

The main advantage of IV infusion is that it allows high IG doses to be given, which can be important for some patients. Also, IG therapy only needs to be given every 3 or 4 weeks when administered IV. Some people may prefer this longer time between doses.

However, a disadvantage is that each IV infusion takes 2–4 hours, or longer, usually in a hospital or clinic attended by a physician or nurse. Sometimes IV infusions can be given at home by a nurse or trained relative. Also, this route requires access to a suitable vein and some patients may feel unwell during or after IV infusions (see below).

In some cases, a tube (or 'catheter') is inserted into a vein and left in place in order to allow easier access for IVIG therapy. This is called an 'indwelling' or 'implantable' catheter. Although they can be useful in some situations, indwelling catheters increase the risk of infections and blood clots, and they can fail and require replacement. They are not suitable for routine use in people with PIDs.

Subcutaneous (SC) infusion

This is where IG is given under the skin of the leg, belly or arm using either a needle and a portable infusion pump ('syringe driver') or a manual rapid 'push' technique.

SC infusions only take 1–2 hours and so may be more convenient. However, only small IG doses can be given by SC infusion. This means that most SC infusions must be given more frequently than IV infusions – usually at least once a week. Larger SC doses can be given using more than one injection site. A new type of SC infusion contains recombinant human hyaluronidase to enhance the flow of IG into the SC tissue and the bloodstream. Known as facilitated SCIG (or FSCIG), this allows patients to have SC infusions every three or four weeks, similar to frequency of IV infusions.

'Rapid push' administration is preferred by some patients, as it can offer even greater convenience and flexibility than infusions using a pump. This method uses a syringe to push the IG solution through a tube and under the skin of the injection site via a needle. The rapid push technique typically uses a smaller IG dose taken every day, and takes only a few minutes. However, not all patients are physically able to do this.

SC administration, by infusion or rapid push, is useful when there are problems in giving IV infusions, for example when a suitable vein is not available. SC therapy can often be given at home by patients themselves, or by parents and carers,

once they have been trained appropriately. Finally, SC administration is less likely to cause some side effects than IV administration (see below).

If the route of administration of IG is changed, from IV to SC or vice versa, the total IG dosage given might need to be adjusted – this is something to discuss with your physician.

THERAPY IN HOSPITAL OR AT HOME?

Clearly, an important consideration is whether your IG replacement therapy is to be given at a hospital or clinic or at home, perhaps even by you, your parent or your carer.

HOSPITAL OR CLINIC THERAPY

Hospital- or clinic-based administration can be helpful if the healthcare team needs to monitor you with particular care, for example when you first start IG therapy or if you have a number of health problems for which you need special care. It is also suitable if you would find it difficult to administer your own IG therapy and if no-one else can give it to you at home.

HOME AND SELF-THERAPY

Once stabilised on IG therapy, many patients prefer to receive this at home instead of at the clinic or hospital. Home therapy can be more flexible and allow patients to be more independent when planning their own care. This also means that patients do not have to miss work or school because of their IG therapy. Home therapy may also be a useful option for patients who have problems attending a clinic owing to distance or problems with transport or mobility.

With support, many adults, young people and even children can learn to administer SCIG themselves at home. Your healthcare team will teach you how to do this and you can find information at the International Patient Organisation for Primary Immunodeficiencies (IPOPI) website (see the booklet “SCIG Infusions – a practical guide for patients” at www.ipopi.org). However, IG must be given carefully at the correct dose on a regular basis and this form of administration is not suitable for everyone, especially if compliance or side effects are likely to be a problem. The dose of IG is calculated on an individualised basis for each patient and so it must be given exactly as prescribed. The infusions must be administered at the correct rate (i.e. over the correct period of time) and should not be speeded up, as this can increase the risk of side effects. It is very important that patients have their IG infusions regularly according to the prescribed schedule so that the level of IG in the blood is sufficient to protect against infections.

Patients, parents or carers must be willing and able to be trained in preparing and administering the infusion according to the prescribed dosage schedule, as well as the necessary aspects of hygiene, storage and disposal of the infusion and supplies. Patients and carers will also need to report any problems to the healthcare team, and to keep a record of the therapy given. Some computer apps to help patients manage their therapy and keep records have recently started to become

available. Home therapy may not be appropriate for patients who have complicated medical needs or who have a history of infusion reactions.

Whether home-therapy and self-therapy are suitable for you is something you should discuss with your physician and nurse.

MONITORING AND FOLLOW-UP

Even if IG replacement therapy is given at home, regular contact with your PID healthcare team is still important! Regardless of which type of IG therapy you have, your healthcare team will need to see you at regular intervals to check for side effects, assess your self-therapy technique (if you are using self-care) and do other assessments according to your individual needs. The dose of IG is initially calculated on an individualised basis for each patient, according to their weight. It may then be adjusted according to the patient's response. In some situations the dose may be adjusted based on a measurement of the lowest level of IG in the blood at the end of a dose cycle, i.e. before the next dose is due. This is known as the 'trough level' and the aim is to ensure that this is at the right level to protect against infection.

WHICH FORMULATION IS BEST FOR ME?

Some patients with PIDs do not experience side-effects from IG replacement therapy. However, others may experience side effects such as headache, light-headedness, chills, fever and joint pains. In some cases, the side effects are mild. In rarer instances, severe effects, including aseptic meningitis (a serious inflammation of the lining of the brain) or even anaphylaxis (a type of severe allergic reaction), may occur.

These side-effects are less common when IG therapy is given SC, compared with IV. This is because these effects are related to the level of IG in the blood. Therefore, SC administration may be more suitable for patients who have previously experienced such side effects, or who are more likely to experience them. On the other hand, SC infusions can cause swelling and pain at the injection site, as well as the other side effects above.

Whether a particular IG product is right for you can depend on its ingredients and formulation. Factors to be considered when choosing between products include:

- Infusion volume: formulations with a larger fluid volume should be avoided in patients who have to limit their fluid intake (for example because of heart failure, high blood pressure or kidney disease) and in infants.
- IG concentration: the concentration of IG in products varies between 3% and 20%, depending on which products are available in your location. Higher concentrations can be useful when higher doses need to be given. However, high concentrations of IG should be avoided in patients at risk of cardiovascular disease.
- Immunoglobulin A level: this should be as low as possible for patients with any history of severe hypersensitivity reactions, including anaphylaxis. Some patients with immunoglobulin A deficiency can have severe reactions to immunoglobulin A.

- **Stabilisers:** these ingredients (most often sugars) are added to ensure that the IG remains dissolved in the infusion solution. The type and concentration of stabilisers used in IG products can affect how suitable they are for certain patients.
 - Sucrose: this should be avoided in patients at risk of kidney complications.
 - Glucose: this should be avoided in patients with diabetes.
 - Maltose: blood glucose monitoring systems can falsely recognise maltose as glucose, distorting glucose readings.
 - Sorbitol: IGs containing sorbitol should not be used in people with diabetes and those with fructose intolerance.
 - Amino acids (L-proline and glycine): products containing L-proline (one of the amino acid 'building blocks' from which the body makes proteins) should not be used in patients who already have high levels of proline in the blood (called 'hyperprolinaemia'). Glycine can cause nausea, vomiting, excessive sweating, headache and fever. Generally, amino acids should be avoided in patients with history of severe allergic reactions and those with certain metabolic disorders that require the intake of particular amino acids to be limited.
- **Sodium:** IG products now contain little sodium — this is important to minimise the risk of side effects related to cardiovascular and kidney disease.
- **Formulation:** IG products are mostly presented as solutions but some come in a 'lyophilised' form (a type of freeze-drying) and need to be reconstituted according to the manufacturers instructions.
- **Osmolarity or osmolality** (measures of the amount of chemicals dissolved in a solution) and **pH** (a measure of the acidity or alkalinity of a solution): these factors can influence the side effects of IG, although most products are now similar in these respects.
- **Allergies:** you should ensure that your physician knows about any allergies you have, especially if you have ever had a severe reaction to any IG product.

PRICE AND AVAILABILITY

IG products are available in many countries, although the range of available products varies. You can see a list of products available in each country, together with their ingredients and properties, at www.ipopi.org.

IG replacement therapy is often provided by centres that specialise in treating PIDs. The way IG therapy is paid for (or 'reimbursed') by the healthcare system varies between different countries and healthcare insurance plans. Moreover, the costs and reimbursement policies may vary between different IG therapies. Patients, parents and carers will need to check their local situation and healthcare plan and take advice from their doctor. Patients can also contact their national patient organisation (via www.ipopi.org) for further information.

IPOPI believes that PID patients should have continuous and equal access to the widest possible range of safe and effective IG therapies. Prescribing physicians should always have the flexibility to choose the most appropriate therapy for individual patients.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 56 countries worldwide, please visit www.ipopi.org.

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