BLOOD ISSUES

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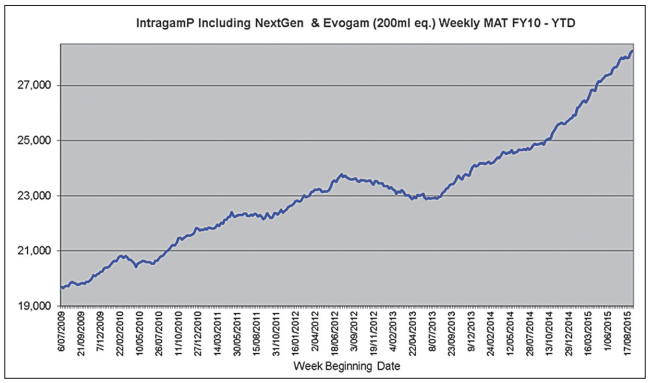
IMMUNOGLOBULIN USE IN NEW ZEALAND

During the last 2 years clinical use of immunoglobulin products in New Zealand has been growing at approximately 13% per annum. This rate of growth is significantly higher than was seen in the previous 5 years as shown in the graph below.



Immunoglobulin use in New Zealand during the 2014/15 financial year was just over 333,000 grams with a financial value of over $29 million.

New Zealand has been one of the few OECD countries that has been self-sufficient for immunoglobulin i.e. all clinical requirements have been met from product derived from plasma collected in New Zealand. The current rate of growth is however outstripping the collection capacity of NZBS and is leading to increased pressure on supply. The NZBS Board have recently approved a recommendation to introduce a commercial immunoglobulin product in order to improve resilience in the supply chain and ensure that all patient needs can be met in a timely manner. This edition of *Blood Issues* focuses on the use of immunoglobulin and aims to provide background information to support the introduction of the commercial product.

The International Picture

New Zealand remains a relatively low user of immunoglobulin products, currently running at 73g/1000 population. In comparison, Australia used 172g/1000 population during 2013/14 and demand there continues to grow at a rate of 11% or more.

Overview of IVIg Use in New Zealand

During 2013 a total of 1165 patients in New Zealand received an immunoglobulin product (IVIg or subcutaneous IgG). The products are used for two main sets of diseases.

The first involves immunoglobulin replacement treatment in patients who are unable to produce immunoglobulins (immunodeficiency) leading to an increased susceptibility to infection. If untreated, chronic infection will lead to organ damage and a progressive decline in overall health status. Recurrent infections, even if adequately treated with antibiotics, reduce quality of life and leads to resource and cost implications for national health care.

Immunodeficiency can either be primary (present from birth with an underlying genetic defect in the immune system) or secondary to a disease that damages a previously normal immune system (usually seen in haematological malignancies such as chronic lymphocytic leukaemia, lymphoma or myeloma). In both types of disorders treatment with immunoglobulin enables normal immunoglobulin levels to be maintained and significantly reduces the likelihood of infections occurring. Immunoglobulin replacement is required on a regular (3-6 weekly) cycle to maintain immunoglobulin levels and following diagnosis is required on a long term (often life-long) basis. Approximately 50% of immunoglobulin treatment in New Zealand is used in this setting.

The second set of indications for immunoglobulin treatment involves its use as an immunomodulatory agent. There is increasing evidence that a range of disorders arise as a consequence of disturbances of the immune system leading to damage to tissues or organs (auto-immune disorders). Immunoglobulin treatment can influence the course of many of these disorders. This type of treatment can either be a short term measure to control disease whilst longer term interventions, such as immunosuppressive agents, take effect or in some settings can be used on a long term basis when the dose of immunoglobulin is modified based on the level of symptoms or objective measures of disease progression. Short term use of immunoglobulin in an immunomodulatory setting is most commonly used in Guillain-Barre syndrome (an acute demyelinating polyneuropathy), in autoimmune thrombocytopenia (ITP) and in Kawasaki disease in children. Long term use of immunoglobulin in the immunomodulatory setting has been particularly successful in a range of chronic neurological disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy.

Currently Available Immunoglobulin Products

NZBS currently provides two immunoglobulin products. Intragam®P is an intravenous immunoglobulin and accounts for 90% of total immunoglobulin use.

Evogam® is a subcutaneous product that can be self-administered by patients at home and is increasingly used by patients with primary immunodeficiency. A small number of patients who are intolerant to the domestic products are treated with commercial products sourced from CSL Behring Australia. Commercial products currently account for less than 1% of total immunoglobulin use.

NZBS will be introducing a commercial intravenous immunoglobulin product, Privigen®, in November 2015. Further information on the product is provided below.

At this stage Evogam® will continue to be provided for all patients requiring subcutaneous treatment. Hizentra®, a product produced by CSL Behring in Europe and the US, is used by a very small number of patients who are unable to tolerate Evogam. This will continue but at this stage NZBS has no plans to introduce a commercial subcutaneous product for routine use.

Privigen®

Privigen® is an intravenous immunoglobulin product manufactured by CSL Ltd in the United States and Europe using plasma from paid donors.

The product is authorised by Medsafe for distribution in New Zealand and is also approved by a number of other regulatory agencies including the USFDA, Australian TGA and the UK MHRA. It is used extensively in Europe, the US and Canada and will be introduced into Australia later this year. A copy of the product datasheet can be obtained on the Medsafe website http://www.medsafe.govt.nz/profs/datasheet/p/privigeninj.pdf.

The approved clinical indications for Privigen® are very similar to those of Intragam®P. The safety and effectiveness of the two products are also essentially the same. This includes broadly similar approved indications for use and adverse reaction profiles of the two products. There are however, some key differences between the two products. These are shown in the table below.

	Intragam®P	Privigen ®
Concentration	6%	10%
Vial sizes	3g, 12g	5g, 10g, 20g
Infusion rate	See product datasheets	

Which Patients will Receive the Commercial Product?

NZBS will adopt an approach similar to that used in Australia. This aims to ensure that regular recipients of IVIg will continue to receive Intragam®P. Privigen® will be used in patients who require IVIg treatment for acute and short term use. This will include patients who have intermittent treatment for ITP and similar conditions.

Adverse reactions are relatively common in patients who receive IVIg products. These are often associated with faster rates of infusion. Common adverse reactions include chills, headaches, fever, vomiting and allergic reactions. The datasheets for both Intragam®P and Privigen® identify that the risk of adverse reactions is increased in patients who receive IVIg for the first time and, in rare cases, when the products are switched or where there has been a long interval since the previous infusion. This is the main reason for aiming to maintain regular recipients of IVIg on Intragam®P.

Initially Privigen® will only be issued to patients receiving treatment at the 6 DHBs where NZBS manages the hospital blood bank. Together these DHBs account for over 80% of national use of immunoglobulin. This approach will simplify stock management at the other DHB blood banks where overall use of the products is relatively low.

Privigen® will be introduced during November 2015. At the point of introduction, patients already receiving Intragam®P will continue on the product. The decision on which product new patients will receive will be made when approval for treatment is obtained from NZBS. Information will be held in e-Progesa (the NZBS blood management system) to ensure that the correct product is provided for each patient.

NZBS estimates that this approach will result in Privigen® making up approximately 18% of total immunoglobulin use in New Zealand.

Approval for Use of Immunoglobulin

NZBS has an approval process in place for immunoglobulin. The process currently varies between individual DHBs. An approval form is used at most of the DHBs where NZBS manages the Blood Bank to facilitate this process. The form can be accessed on the Blood Resource site on the DHB intranet (https://www.clinicaldata.nzblood.co.nz/resourcefolder/documents/111F075.pdf). The form has been updated to support the introduction of Privigen®. Clinicians will be notified as to which immunoglobulin product will be provided for a patient at the point that approval for supply is provided.

Impact, Informed Consent, Prescribing and Administration

NZBS is updating the informed consent leaflets for immunoglobulin treatment to identify that both Intragam®P and Privigen® are in use in New Zealand.

Intragam®P and Privigen® have different concentrations and dose sizes. This means that prescriptions for immunoglobulin must clearly identify which product is to be used. This also applies when the product is ordered from NZBS.

In the event that NZBS receives an order for Intragam®P when the patient has been allocated Privigen® then we will contact the doctor responsible for the request and

seek permission to provide Privigen®. This is necessary in order to ensure compliance with the requirements of the Medicines Act and Medicines Regulations.

The Transfusion Nurse Specialists will provide support for issues arising within clinical areas and will also proactively undertake education and training of nurses in areas where immunoglobulin is used frequently.

An Audit of Intragam P® Use in New Zealand

During 2014, NZBS undertook an audit of the use of Intragam P® involving 10 DHBs. These 10 DHBs account for 72% of all Intragam P® issued in New Zealand.

The audit assessed compliance against two sets of guidelines. These were the Australian National Blood Authority (NBA) Criteria for the clinical use of intravenous immunoglobulin in Australia (second edition 2012) and the United Kingdom Department of Health Clinical Guidelines for Immunoglobulin Use, initially published in 2011. Both guidelines can be accessed via the Blood Resource sites on DHB intranets (https://www.clinicaldata.nzblood.co.nz/resourcefolder/selectdhb.php).

891 treatment episodes (used in a new clinical indication) in 864 patients were audited. Based on the results of a previous audit undertaken in 2004/05, 5 clinical indications were assessed in detail against both guidelines. Together these 5 conditions accounted for 75% of total Intragam®P use in the 10 hospitals. The results for these 5 conditions are shown in the table below.

Diagnosis	% total use	% Patients complying with Australian Qualification Criteria	% Patients complying with NHS Qualification Criteria
Primary Immunodeficiency	30%	88%	88%
Secondary Immunodeficiency	18%	45%	5%
CIDP	16%	72%	38%
ITP	6%	94%	92%
Guillain-Barre Syndrome	6%	74%	75%
Other disorders	24%	74%	81%
Total	100%	73%	64%

The criteria utilised in both sets of guidelines are reasonably similar having two main sets of criteria. The first set focuses on the clinical indication for use of the product and identifies specific criteria that should be met before treatment is commenced. The second set of criteria focus on review of patients following a period of treatment with IVIg and identify criteria that should be met to support on-going treatment with the product.

The qualification criteria for Primary Immunodeficiency Disorder (PID) requires the diagnosis to be made by a clinical immunologist and for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) by a neurologist. Additional qualifying criteria exist for each indication. The failure to meet the requirement for a specific specialist to establish the diagnosis is in part responsible for the identified non compliances. Significant differences were identified in the level of compliance with qualification criteria by DHB. Many of the patients will have been on Intragam®P for many years and the quality of earlier medical record keeping are not always of the standard expected today. In smaller DHBs compliance was often lower. It is likely that a diagnosis might have been discussed and supported with a relevant specialist but this might not have been identified as part of the audit. Whilst acknowledging this, the audit does suggest that a more pro-active method for capture of clinical information and a more formal approach to evaluation of suitability against current guidelines might assist in more appropriate use of the product moving forward.

The same issues apply to the review criteria. Summary results are shown in the table below.

Diagnosis	% total use of product	% Patients complying with NBA Review Criteria	% Patients complying with NHS Guidelines Review Criteria
Primary Immunodeficiency	30%	No review criteria set	
Secondary Immunodeficiency	18%	73%	89%
CIDP	16%	75%	77%
ITP	6%	100%	97%
Guillain-Barre Syndrome	6%	89%	80%
Other disorders	24%	67%	74%
Total	100%	76%*	82%*

*excludes PID patients

Ensuring Appropriate Use of Immunoglobulin

NZBS utilises a pre-approval process for accessing Intragam®P. Currently this is managed differently at each DHB. Requests for the product are assessed against the guidelines but the qualification criteria contained in the guidelines are not currently strictly enforced. A number of DHBs have indicated a desire to move to a more formal process for accessing these products. Tools for simplifying peer or expert review at the initiation and review of Intragam®P treatment can be expected to improve compliance. This would also assist the smaller DHBs whose use appears to be climbing at a faster rate than the larger DHBs, as well as larger DHBs who see a large financial outlay associated with the use

of Intragam®P. Introduction of this type of process will require agreement with participating DHBs. This would require identification of a specific set of qualification and review criteria and a process for review of requests falling outside of the criteria. The Australian guidelines will likely be most appropriate given the close clinical contacts between New Zealand and Australia. NZBS is currently developing an electronic approval process which will provide better information and enable easier reporting to DHBs and this could form the first step in the development of a broader governance process.

Accessing More Information

Information on the immunoglobulin products provided by NZBS can be found on the Blood Resource website. The site is managed by NZBS and can be accessed via the DHB intranet system. The sites can also be accessed via the intranet at https://www.clinicaldata.nzblood.co.nz/resourcefolder/selectdhb.php

Update on Introduction of 7 Day Platelets

In the April edition of *'Blood Issues'* NZBS announced their intention to introduce platelet components with a seven day shelf life. The extension of the shelf life from five to seven days is made in conjunction with the implementation of a comprehensive bacterial screening programme. The changes will enhance the safety of platelet components by reducing the risk of bacterial contamination and the extended shelf life will allow improved utilisation of platelet products. The approach that is being used by NZBS mirrors systems in place at the English National Blood Service. Haemovigilance data from the UK indicates that the longer shelf life does not impact adversely on safety or efficacy.

The changes required to support the implementation of seven day platelets have progressed as planned. Implementation at the Auckland Blood Centre commenced on 21st September 2015. This is being used as a pilot in order to support enhanced monitoring, both clinical and quality, as required by Medsafe. The timeline for national implementation will be determined once the results of the pilot have been reviewed. NZBS hopes to be able to complete the national implementation prior to Christmas in order to ensure maximum benefit from the extended shelf life over the main holiday period.

For more information on the risks of bacterial contamination of platelets and the likely clinical impact of the extended shelf-life of the components refer to the April edition of *'Blood Issues'*.

2014 Haemovigilance Report

The 2014 Annual Haemovigilance Report will be available for distribution during October 2015. The report will be available on the NZBS website (www.nzblood.co.nz). Requests for hard copy versions should be sent to Jillian.Sinden@nzblood.co.nz.

Use of Rh (D) Immunoglobulin in Patients with a Body Mass Index ≥30

Earlier this year CSL Behring Australia updated the Rh (D) Immunoglobulin Product Information to include a recommendation that the clearance of fetal cells and the presence of Rh (D) antibody be confirmed post-administration in patients with a BMI ≥30. This change generated questions from healthcare professionals regarding the implications for clinical and laboratory practice.

The Australian Red Cross Blood Service and the Australian National Blood Authority convened an expert panel to review the evidence behind the changes recommended by CSL Behring Australia and to develop appropriate actions. NZBS was included in the expert panel review.

The Consensus recommendations arising from the process identified that whilst there is some evidence to suggest that intramuscular administration of Rh (D) Immunoglobulin may be associated with an increased risk of lack of effect in patients with a BMI ≥30, the data is currently insufficient to support a change to clinical and laboratory practice. A number of specific recommendations were made:

- It is important that a recommendation is made to all Rh (D) negative women to receive Rh (D) Immunoglobulin in accordance with currently established guidelines (NZBS guidelines for this can be accessed via the Blood Resource website on DHB intranets https://www.clinicaldata.nzblood.co.nz/resourcefolder/selectdhb.php).
- The CSL Rh (D) Immunoglobulin must be given by deep intramuscular injection. For women with a BMI ≥30 particular consideration should be given to factors which may impact on the adequacy of the injection, including the site of administration and the length of needle used.
- No specific additional testing is required because a woman has a BMI ≥30. Routine post-administration testing is not required unless there has been a large feto-maternal haemorrhage (FMH); in which case testing should be in accordance with current established guidelines.
- For women with a BMI ≥30 who experience a FMH of greater than 6ml, consideration may be given to administering any additional required doses via the intravenous route (NZBS supplies Rhophylac® for this purpose), to facilitate the more rapid clearance of fetal cells.

A full copy of the Consensus Statement is available on the Blood Resource website on DHB intranets https://www.clinicaldata.nzblood.co.nz/resourcefolder/selectdhb.php).