

BLOOD ISSUES

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Intragam® P Audit in New Zealand

The place of the Intravenous Immunoglobulin (IVIG) as replacement therapy in patients with primary and secondary immune deficiency is well established. IVIG is also widely employed as first line or adjuvant therapy, or as an alternative to immune suppressants or plasmapheresis, in a variety of diseases attributed to an immune aetiology. As a result it is currently the most widely used plasma product in the world. The use of IVIG in immunomodulatory settings is supported by lower levels of evidence than its use in replacement therapy. The relative ease of IVIG therapy is a factor in influencing its choice ahead of other established options.

The widespread off-label use of IVIG has become an urgent problem in some countries. It has been stated that the same policy that is used for other high cost treatments should be used for IVIG as well, i.e. the application of such therapy should be based on proven efficacy such as controlled, double blind clinical trials. If such a criterion was applied then a significant percentage of off-label indications are found to lack an evidence base. However it is recognised that for some particularly rare disorders, controlled clinical trials may not be feasible and examination of other lesser levels of evidence may be necessary. Presently, there are no generally accepted guidelines for the use of IVIG in New Zealand. In 1992, the Australasian Society of Blood Transfusion (ASBT) convened a consensus symposium to discuss the indications for use of IVIG and to formulate a list of recommendations for its use. Evidence for the efficacy of IVIG for each reported indication was assessed on the basis of the reported study type, the findings and the number of people in each particular study. The outcome of the symposium was a set of consensus guidelines (referred to as the 1992 guidelines) which grouped indications for the use of IVIG into three categories:

Category A: Diseases and situations where the use of IVIG is indicated

Category B: Potentially severe diseases or situations where IVIG may have a role

Category C: Clinical conditions where the evidence for benefits derived from the use of IVIG was either conflicting or anecdotal such that the use of IVIG in those conditions could not be justified.

In 2000, a national review of the use and supply of IVIG by the Australian Health Minister's Advisory Council (AHMAC) Blood and Blood Products Committee resulted in a report that made recommendations that included, the adoption of a national policy for the clinical use of IVIG based on a new categorisation of clinical indications:

Category 1: Indications for which there is now convincing evidence of benefit

Category 2: Indications for which there is inconclusive evidence of benefit

Category 3: Conditions for which there is convincing evidence that IVIG has no benefit

Also responding to the increased demand for Intragam® P, the Auckland District Health Board established an IVIG committee that identified specific criteria for treatment with IVIG and developed recommendations for appropriate use. These recommendations go further than the AHMAC guidelines in that they identify not only diseases where IVIG might be appropriate but also identify specific criteria for treatment with IVIG.

In New Zealand, Intragam® P is licensed for use as replacement IgG therapy in primary immunodeficiency; myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; and congenital or acquired immune deficiency syndrome with recurrent infections. It is also licensed for use for immunomodulatory therapy in idiopathic thrombocytopenic purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count; allogeneic bone marrow transplantation, Kawasaki disease and Guillain Barré Syndrome.

Audit Method

In 2005 the New Zealand Blood Service carried out an audit to determine whether the usage of Intragam® P in New Zealand conforms to the AHMAC guidelines and the ADHB guidelines. The audit included those patients who receive Intragam® P as an inpatient or outpatient. DHBs participating in the audit were Auckland, Waikato, Bay of Plenty, MidCentral, Capital & Coast, Canterbury, Otago and Southland. Relevant clinical details of each patient were reviewed once only unless the clinical indication changed. Data collection for each episode included patient demographics (Progesa number, NHI number, age, gender and weight), product data (the date of issue and the total course dose) and clinical data (the clinical diagnosis, the severity of the disease, blood tests where applicable and the AHMAC guidelines category).

The data was collated in a Microsoft Access database with restricted access, located on NZBS's internal network. No patient identifying data was included. On completion of the audit, the national blood management computer system, Progesa, was searched for the total dose received during the six months of the audit, the first ever date that the patient was recorded as having received Intragam® P and the first date the patient was tested for ABO blood group.

There were six Transfusion Nurse Specialists and a Medical Officer collecting data and this methodology permitted a multi-centre audit to be performed. Access to old notes and laboratory results was often difficult, due in part to changing computer systems and paucity of notetaking.

Assessment of some patient's diagnoses and their condition at commencement of Intragam® P was not as robust as others, particularly for a number of patients with antibody deficiencies.

RESULTS

AHMAC Categories

The majority (81%) of all episodes were in AHMAC category 1 (indications with convincing evidence of benefit) (table 1). 13% of episodes had a diagnosis not listed in the AHMAC guidelines or did not meet the criteria set down by the AHMAC guidelines.

Table 1. Breakdown of episodes by AHMAC categories

| AHMAC Category | Percentage n=466 |
|---|------------------|
| Category 1 Indications with convincing evidence of benefit | 81% |
| Category 2 Indications with inconclusive evidence of benefit | 5% |
| Category 3 Conditions with convincing evidence that IVIG has no benefit. | 1% |
| No AHMAC category listed | 13% |

Of the 19% of episodes that were not in Category 1 of the AHMAC guidelines half were from diagnoses recognised by the ADHB guidelines. However the remaining half were an assortment of diagnoses, largely with a single patient per diagnosis.

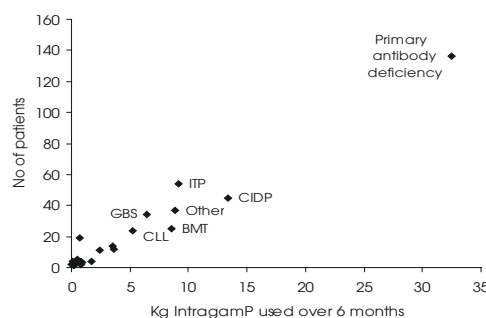
Comparison of AHMAC Category 1 episodes with ADHB Guidelines episodes

Although the ADHB guidelines had not been distributed outside ADHB until this audit, they appear to be covering the majority of patients at all DHBs with 72% of cases meeting the ADHB guidelines for Intragam® P use (table 2).

Table 2. Episodes meeting the draft ADHB guidelines

| DHB | n | Meet ADHB Criteria | Meet AHMAC Category 1 |
|-----------------|-----|--------------------|-----------------------|
| Auckland | 139 | 88% | 89% |
| Bay of Plenty | 31 | 61% | 84% |
| Canterbury | 71 | 65% | 75% |
| Capital & Coast | 76 | 72% | 83% |
| MidCentral | 22 | 55% | 82% |
| Otago | 35 | 57% | 71% |
| Southland | 27 | 56% | 70% |
| Waikato | 65 | 68% | 74% |
| Overall | 466 | 72% | 81% |

Figure 1. Total Intragam® P Issues by Patient



Conclusion

The sustained rise in Intragam® P use is of concern both to blood services and funders, locally and internationally.

This audit has shown that although a significant amount of Intragam® P is used for off-label indications, 81% of issues of Intragam® P met the requirements for category 1 in the AHMAC guidelines but only 72% met the criteria for the draft ADHB guidelines. Using Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as an example, Intragam® P would be accepted under AHMAC guidelines provided there was objective improvement at 3 months. The ADHB guidelines require sufficient weakness to interfere with important activities and having either failed steroids or not been able to use steroids (intolerant or contra-indicated).

The majority of Intragam® P use is restricted to very few diagnoses (figure 1). Together, primary antibody deficiency, CIDP, ITP and Guillain Barré accounted for 59% of all patients and 61% of all Intragam® P used over 6 months. Similarly, high volume recipients, defined as receiving the top 3% of doses (either dose per kg per episode or total dose over 6 months), contributed up to a third of some DHBs' total use of Intragam® P. This information can be used to guide strategies to monitor or contain the use of Intragam® P.

Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia. CSL Ltd, the manufacturer of Intragam® P, recommends that all patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) should have a pre-infusion ABO blood group determined and have their haemoglobin monitored in the days following therapy for evidence of clinically significant haemolysis. Only 38% of such patients in this audit had an ABO blood group in the Progesa system.

A little over half of Intragam® P recipients identified in this audit had received Intragam® P prior to the audit as well, suggesting they had indications for chronic or repeated use. These patients accrued at a rate of 11% per year. A smaller component of the rise in use is the chronic or repeated use of Intragam® P in growing children. Only 5% of recipients fell into this group, with their growth potentially accounting for less than half a percent overall increase in Intragam® P.

Hereditary Haemochromatosis

Hereditary Haemochromatosis (HH) causes progressive iron overload and typically manifests in the 5th decade in males and in the 6th decade in females. Females tend to have a less severe form of the disease as a result of iron loss from menses and childbirth. Symptoms of HH are generally non-specific and include fatigue, malaise and arthralgia.

Excess iron can affect many organs:

- Liver – enzyme alterations, fibrosis, cirrhosis and hepatocellular carcinoma (200 fold increased risk if cirrhotic)
- Heart – arrhythmia, failure, cardiomyopathy
- Pancreas – diabetes mellitus
- Pituitary – decreased libido, impotence, amenorrhoea, hypogonadism
- Thyroid gland – hypothyroidism
- Joints – arthralgia, arthropathy, typically the 2nd and 3rd metacarpophalangeal joints
- Skin pigmentation

HH can be divided into 4 stages:

- Genetic predisposition, no other abnormality
- Iron overload (2-5g) no symptoms
- Iron overload and early symptoms
- Iron overload and organ damage

Classic Hereditary Haemochromatosis

More than 90% of people affected by HH in our population have classic (Type 1) HH. This is associated with homozygosity for the C282Y HFE gene mutation (cysteine replaced by tyrosine at position 282) and has autosomal recessive inheritance. The HFE gene is located on chromosome 6 and was cloned in 1996. The function of the HFE protein is not known but probably has a role in the down-regulation of intestinal iron absorption. Since genetic testing became available, an increasing number of patients with early stage HH are being identified, either by cascade screening e.g. first degree relatives of affected individuals, or by opportunistic screening.

The C282Y mutation is thought to have originated in Northern Europe and has a higher incidence in certain populations (Celtic or Viking ancestry). Approximately 1 in 200 are homozygous for the C282Y mutation. It is rare in people of Asian and African ethnicity.

A second mutation of the HFE gene H63D (histidine replaced by aspartic acid at position 63) does not tend to cause iron overload however compound heterozygous haemochromatosis (C282Y/H63D i.e. one of each type of mutation), can cause iron overload (up to 4% of HH) although it is less severe.

Recent evidence suggests that HFE gene mutations have low clinical penetrance and high biochemical penetrance i.e. many C282Y homozygotes have abnormal iron studies (approximately 75%) but low frequency of clinical disease. Population screening is therefore not currently advocated. Studies are now focusing on other genetic and environmental factors that may contribute to differential expression of C282Y

homozygosity. The clinical effect of the S65C (cysteine replaces serine at position 65) mutation of the HFE gene remains controversial.

Other types of Hereditary Haemochromatosis

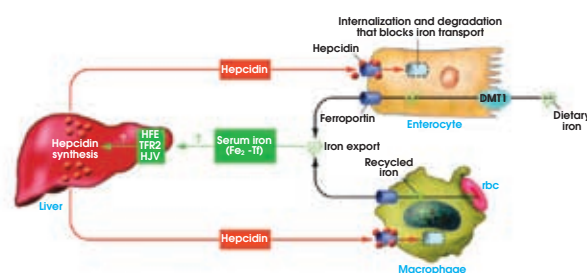
Juvenile haemochromatosis (Type 2) is rare and also has autosomal recessive inheritance but causes a more severe iron overload with earlier onset (second decade). It occurs equally in males and females. Mutations of the hemojuvelin (HJV) gene on chromosome 1 (Type 2A) were identified in 2003 and previously termed "HFE2". The protein is expressed in muscle, liver and heart however its function is not known. Type 2B is caused by mutations of the HAMP (human antimicrobial peptide) gene on chromosome 19. HAMP produces hepcidin, a 25 amino acid peptide gene that is synthesised by the liver and excreted by the kidneys. Type 3 involves mutations of the transferrin receptor 2 (TFR2) gene on chromosome 3 and is also autosomal recessive.

Types 1, 2 and 3 share common pathogenetic and clinical features with HFE HH. However in Type 2 the clinical onset occurs earlier and the phenotype expressivity is more severe than classic HH. Type 4 is an autosomal dominant condition with heterozygous mutations in the ferroportin 1 gene (SLC40A1) on chromosome 2. Type 4 is characterised by predominant reticuloendothelial cell iron overload and milder disease. Other rare genetic defects have been associated with iron loading.

Regulation of Iron Homeostasis

Body iron stores and inflammatory stimuli regulate expression of hepcidin. Diferric-transferrin (Fe_2 -Tf) is detected by the liver via an as yet unknown complex regulatory pathway involving HFE, TFR2 and HJV. Hepatocytes respond to this signal by inducing HAMP expression and hepcidin secretion. Circulating hepcidin regulates iron metabolism by binding ferroportin 1, an iron export molecule on intestinal epithelial cells and macrophages. Hepcidin induces internalisation and subsequent degradation thus decreasing dietary iron absorption in the enterocytes and reduced iron recycling by macrophages. In classic and juvenile haemochromatosis the mutations in HFE, TFR2 and HJV lead to abnormal hepcidin regulation, hepcidin deficiency (partial in Type 2 and complete deficiency in HJV homozygous mutations) and ferroportin hyperactivity. (DMT 1 = divalent metal transporter 1)

Regulation of systemic iron homeostasis



vaouout, S. et al. Clin. Invest. 2005; 115: 2079-2082

Hypohepcidinaemia – A Unifying Pathogenetic Cause

Recent studies have demonstrated that the pathogenesis of nearly all forms of HH involve inappropriately decreased expression of the iron-regulatory hormone hepcidin. Studies show that HJV^{-/-} mice have virtually undetectable HAMP mRNA in their livers, earlier and more advanced liver iron deposition and ferroportin over expression in intestinal cells and macrophages.

Patients with juvenile haemochromatosis (HJV or HAMP mutations) have low or undetectable urinary hepcidin. Patients with C282Y haemochromatosis have inappropriately low hepcidin levels for the degree of iron loading. Similarly reduced levels were found in patients homozygous for TFR2 mutations. Conversely over expression of hepcidin in transgenic mice caused iron-deficient anaemia. In addition, hepcidin over expression in iron overloaded mice reduced ferroportin expression and induced redistribution of hepatocyte-stored iron to Kupffer cells.

Laboratory Testing

HFE gene mutation analysis is indicated in:

- patients with symptoms of HH and abnormal iron studies (elevated transferrin saturation and serum ferritin)
- first degree relatives of probands
- people with incidental abnormal iron studies
- liver disease

Iron studies:

- a persistent fasting transferrin saturation >45% is the best initial phenotypic screening test
- serum ferritin is a good indicator of body iron stores although can be elevated in the presence of inflammation or hepatic necrosis
- normal serum ferritin and transferrin saturation have a negative predictive value of 97%

Assessment of Hepatic Iron

Prior to the availability of the HFE gene mutation tests, diagnosis was based on liver biopsy. It still has an important prognostic role. A calculated hepatic iron index (dry weight iron/age in years) >1.9 indicates iron overload. In addition liver biopsy can assess distribution of iron e.g. parenchymal/periportal in classic HH, and in Kupffer cells in 2^o iron overload or type 4 HH. Liver histology will also identify cirrhosis, which has implications for screening for hepatocellular carcinoma.

General indications for liver biopsy include abnormal liver function tests, ferritin >1000ng/mL and age >40 years. T2-weighted magnetic resonance imaging (MRI) provides a non-invasive evaluation of liver iron burden (decreased signal intensity). Comparative studies have shown excellent concordance of results between MRI and liver biopsy. The MRI scanner requires specific calibration for assessing iron deposition, however it has the advantage of examining the entire liver. Secondary iron overload and ferroportin diseases can result in iron deposition in the reticuloendothelial system, where low signal intensity is seen in both the liver and the spleen.

Treatment

Life expectancy is normal if iron reduction is initiated before the development of irreversible manifestations such as cirrhosis, hypogonadism and arthropathy. Iron is removed by regular phlebotomy, usually initially weekly if tolerated. In general each unit (470mL) contains 200 – 250mg iron. Individual phlebotomy volumes and frequency are adjusted according to the patient's age, mass, haemoglobin level, comorbidities and donor status. Full blood count and iron studies are tested after each 1 – 2g iron removed. When the serum ferritin reaches 50ng/mL and the iron saturation <50% the frequency of phlebotomy is reduced to approximately 4 per year but must continue indefinitely to prevent reaccumulation of iron. The complications of phlebotomy are the same as for donating blood. It is a relatively safe, inexpensive and effective treatment. Phlebotomy has been shown to reverse hepatic fibrosis, improve fatigue, skin pigmentation and hypertransaminasaemia. Diabetes progression can be slowed. In rare circumstances where venesection is contraindicated, iron chelation by subcutaneous desferrioxamine may be used.

Patients should avoid excessive intake of iron-rich foods, vitamin C and alcohol. Iron supplementation must be avoided. Six monthly screening for hepatocellular carcinoma by alpha-fetoprotein level and liver ultrasound scan should be undertaken in patients with cirrhosis. β blocker prophylaxis is recommended in patients with portal hypertension and varices. Liver transplantation has been performed for end-stage liver disease secondary to haemochromatosis. Available evidence indicates that the fundamental abnormality is reversed by successful liver transplantation. There is no reaccumulation of iron if the donor liver is from an HFE-normal subject with normal iron studies.

"IRONZ" is the New Zealand Haemochromatosis Awareness and Support Group. Contact details are available on their web-site www.ironz.org.nz.

Blood Donation

The majority of patients with HH are identified at an early stage prior to organ damage. Blood collection from these patients do not pose a risk to transfusion recipients. Following a medical assessment which includes liver function tests such patients may be eligible to become voluntary whole blood donors. The usual donor criteria must be met and the patient/donor needs to complete a special health questionnaire and sign the standard donor consent prior to each donation. However the frequency of donation is based on iron levels and may be more or less frequent than the 12 week interval for regular blood donors.

Further information and guidelines for referral for Therapeutic Venesection are available at all New Zealand Blood Service Collection sites.