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Immunoglobulin therapy

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ABSTRACT

Immunoglobulin is an expensive blood product of potentially limited supply used in a wide variety of medical conditions, across a number of specialties. Historically, immunoglobulin has been associated with transmission of blood borne infection (eg hepatitis C). Immunoglobulin use needs to be carefully considered, appropriately prescribed and recorded. The Department of Health, in conjunction with relevant stakeholders, has established a demand management programme to secure immunoglobulin supplies for patients most in need of treatment and to limit use for indications where evidence is lacking.

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Introduction

Immunoglobulin is a blood product, centrally funded by NHS England and used in a wide variety of medical conditions, across a number of different specialties. The aim of this short review is to provide some background into immunoglobulin use, highlight specific issues associated with immunoglobulin therapy and outline the Department of Health's Demand Management Programme.

Immunoglobulin is derived from pooled blood donation. It predominantly consists of IgG, with minimal amounts of IgA and IgM. Broadly, immunoglobulin use can be divided by indication into replacement therapy – for patients with primary and secondary immune deficiency diseases – and immunomodulatory therapy, for treatment of a number of autoimmune and inflammatory conditions.

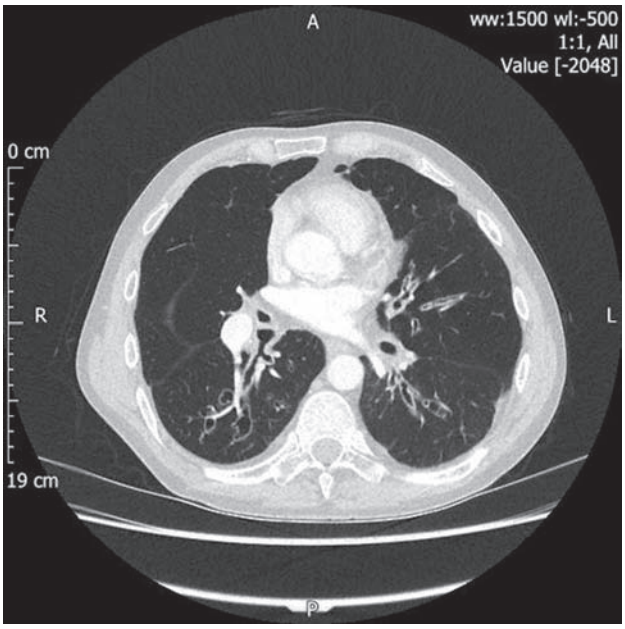

Fig 1. Thoracic computerised tomography confirming extensive bronchiectasis, as evidenced by cylindrical and more peripheral airway dilatation with bronchial wall thickening, in a patient with primary antibody deficiency.

Immunoglobulin replacement therapy

Immunoglobulin replacement therapy is generally straightforward, with the aim of reducing infection frequency and thereby either preventing or minimising the progression of infection-related end-organ damage, such as bronchiectasis (Fig 1). The usual replacement dose is 400–600 mg/kg/month, which can be given intravenously at 2–4 weekly intervals, or more frequently as subcutaneous therapy. A newly developed hyaluronidase linked product for monthly subcutaneous use is not currently routinely funded by NHS England. Treatment efficacy can be measured in terms of infection frequency, trough IgG levels (IgG just prior to an infusion) and, more importantly, clinical outcome.[1,2]

Key points

- Immunoglobulin is a blood product derived from pooled blood donation
- Immunoglobulin is used as replacement therapy for patients with primary and secondary immune deficiency disorders
- Immunoglobulin is used as immunomodulatory therapy in a wide range of autoimmune and inflammatory conditions, with a variable evidence base
- Because of concerns regarding new variant Creutzfeldt-Jakob disease, British plasma is currently excluded as a plasma source for immunoglobulin production
- The Department of Health, with stakeholder input, has established the Demand Management Programme for Immunoglobulin, which includes a national clinical guideline, with the aim of securing supplies for patients most in need of treatment

KEYWORDS: Blood product, demand management, immunoglobulin, immunomodulatory, replacement

Immunomodulatory therapy

Immunomodulatory therapy involves higher dose treatment, usually between 1 and 2 g/kg, administered over 2–5 days per treatment course. The mechanism of action is not clearly defined but may include anti-cytokine activity, blockade of receptors of the reticulo-endothelial system and interaction with the complement pathway.[3] Historically, because of the volumes involved, immunomodulatory therapy has been given intravenously, but more recent high-dose subcutaneous therapy has been successfully applied.[4,5]

Patients on long-term therapy, either replacement or immunomodulatory, can be trained for home therapy, if appropriate. Immunoglobulin should not be prescribed by GPs but rather restricted to the specialist responsible for the patient's treatment.

Concerns

Prior to the recognition of the hepatitis C virus (HCV) in 1989, a number of outbreaks of non-A non-B hepatitis in the 1980s (due to hepatitis C) were associated with the use of particular batches of intravenous immunoglobulin.[6] A number of patients who received a contaminated batch of hepatitis C antibody screened intravenous immunoglobulin in 1993–94 developed serious hepatitis C-related complications.[7] Model-based estimates of blood transfusion in 2000–01, following the introduction of nucleic acid technology screening of blood donors, indicated a per unit risk of 1 in 1,600,000 for HCV transmission.[8] Additional fractionation steps in product preparation, including pasteurisation, nanofiltration and solvent detergent treatment, have become routine to minimise the risk of viral transmission. Extrapolating from the above figures, the risk of HCV transmission associated with immunoglobulin use is now extremely low.

In the UK, because of concerns regarding new variant Creutzfeldt-Jakob disease dating back to the late 1990s, British plasma has been, and remains, excluded as a plasma source for immunoglobulin production. Therefore, we are reliant on imported product in the UK, with inevitable cost and potential supply implications.

National Demand Management Programme for Immunoglobulin

In 2006, the Department of Health set up a demand management programme for immunoglobulin use with the aim of securing immunoglobulin supplies for patients in greatest clinical need, ensuring patients are treated according to appropriate clinical indications, and developing a more evidence-based approach to immunoglobulin use. As a result, trusts across the country should be able to forecast their likely immunoglobulin requirements and thereby avoid treatment

interruption for patients with an absolute treatment need during times of shortage. While it is beyond the scope of this article to cover the whole process, the demand management programme comprises the Demand Management Plan for Immunoglobulin;[9] the national clinical guidelines for immunoglobulin use, implemented in 2008[10] as a cross specialty national guideline and updated in 2011;[11] and the national Immunoglobulin Database.

Clinical indications

Clinical indications are divided into a colour coded system:

- Red indications are diseases for which immunoglobulin is considered the highest priority because of a risk to life without treatment, for example patients with primary antibody deficiency diseases. Such patients have priority in times of shortage.
- Blue indications are those conditions where there is evidence of benefit from immunoglobulin therapy, but for which there may be alternative treatment options, for example plasma exchange in myasthenia gravis. In times of shortage, the alternative treatments should be considered. For some of these conditions, newer treatment options have become more main stream, for example rituximab for certain haematological indications.
- Grey indications are those where the evidence of benefit is limited. These are further divided into diseases that are likely to be immune-mediated with limited evidence of immunoglobulin efficacy, and those that are presumed immune-mediated with little or no evidence of efficacy. This usually applies to rare diseases where clinical trial data are lacking and the evidence base is limited to small case series or single case reports.

Table 1 details some of the more common indications by category.

Treatment is defined as short-term (up to 3 months) or long-term (3–12 months), other than for patients with immune deficiency disorders where potentially life-long treatment is indicated. For patients on long-term treatment, unless there are clinical indications to switch product, it is recommended that a given product is continued. For patients having short-term therapy, unless there are specific indications to consider a specific product, the most cost-effective treatment option is logical. Based on current figures, the average cost of treating a 70 kg patient with a single, high-dose course of immunoglobulin is in the order of £5,000. Immunoglobulin therapy should be approved by the local immunoglobulin assessment panel, which usually includes clinical representatives from the main user specialties, with appropriate pharmacy support. The panel structure will vary by trust or local network. Funding is generally secure for patients with red and blue indications, but for grey indications – in addition to local panel support – individual funding requests are considered on a case by case basis. For further process information, please refer to the Demand Management Plan for Immunoglobulin Use.[9]

There are a number of conditions in which immunoglobulin may be required as emergency treatment, for example Guillain-Barré syndrome, staphylococcal toxic shock syndrome or myasthenia gravis. Treatment should not be delayed in such cases but mechanisms need to be in place locally whereby such emergency patients are registered on the national database with appropriate treatment recording.

Table 1. Examples of immunoglobulin indication by category and duration

Colour	Indication	Duration
Red = high priority	Chronic inflammatory demyelinating polyneuropathy	Short term (blue as long term)
	Guillain-Barré syndrome	Short term
	Immune thrombocytopenic purpura	Short term
	Kawasaki disease	Short term
	Primary immune deficiency	Long term
	Specific antibody deficiency	Long term
	Toxic epidermal necrolysis/ Stevens Johnson syndrome	Short term
Blue = medium priority	Immunobullous disease	Long term
	Inflammatory myopathies	Long term
	Multifocal motor neuropathy	Long term
	Myasthenia gravis	Short term
	Secondary antibody deficiency	Long term
	Staphylococcal/Streptococcal toxic shock syndrome	Short term
Grey = low priority	Autoimmune encephalitis	
	Pyoderma gangrenosum	
	Systemic vasculitides	

Adapted from the Department of Health Demand Management Plan for Immunoglobulin Use

Immunoglobulin Database

As part of the National Demand Management Programme for Immunoglobulin, the national Immunoglobulin Database has been established to record immunoglobulin use according to indication and by specialty, to facilitate management of product shortages, to support immunoglobulin procurement and monitoring, to facilitate safety and recall management (in the event of product contamination), and to support audit and commissioning. Information from the database is the main source of data submitted to NHS England for specialist commissioning. While collection of efficacy outcome data does not currently have a direct financial implication, it is likely to inform longer-term decisions for clinical indications, particularly those in the grey category where evidence of efficacy to date is suboptimal. Over time, certain indications are likely to be reassigned based on the outcome data, or lack of data, reported. It is the responsibility of the prescribing clinician to ensure that outcome data is recorded.

Currently, 165 NHS trusts in England submit data to the national database. Expenditure on immunoglobulin for the financial year 2014–15 was £148 million, based on the Department of Health Commercial Medicines Unit figures (data derived from sales data supplied by the relevant pharmaceutic companies, representing the most complete record). Almost 22 million grams of immunoglobulin have been recorded on the database. The top ten indications are as listed in Table 2, with the main user specialties being haematology, immunology and neurology, as expected (Fig 2).

Table 2. Top 10 diagnostic conditions by usage

Diagnosis	Usage (grams)
Primary immunodeficiencies	1,102,219
Chronic inflammatory demyelinating polyradiculoneuripathy	859,480
Multifocal motor neuropathy	411,494
Other conditions	289,681
Secondary antibody deficiencies	225,445
Immune thrombocytopenic purpura – acture	222,817
Chronic lymphocytic leukaemia	204,527
Myasthenia gravis	173,893
Guillain-Barré syndromes	142,456
Inflammatory myopathies	97,318

Data from MDSAS (Medical Data Solutions and Services)

Conclusions

Immunoglobulin is an expensive and potentially limited blood product used across a range of medical specialties. Its use needs to be carefully considered, appropriately prescribed and recorded. Historically, immunoglobulin has been associated with transmission of blood borne infection (hepatitis C), which – with the current donor screening and viral inactivation steps used in production – is unlikely to be repeated. The National Demand Management Programme for Immunoglobulin has been established to secure immunoglobulin supplies for patients most in need of treatment and to limit use for indications where evidence is lacking. Further information regarding this demand management programme can be found at **www.igd.nhs.uk**. ■

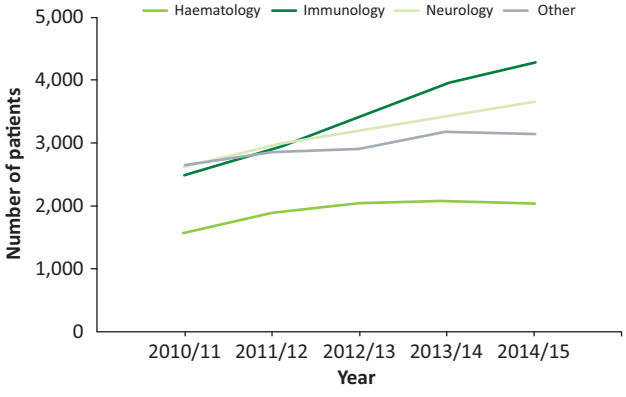

Fig 2. Number of patients treated by specialty 2010–2015. Data from MDSAS.

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