Immunoglobulin Use in Immune Deficiency in the United Kingdom: A Report of the UKPID and National Immunoglobulin Databases

Abstract

The supply of immunoglobulin to patients in the United Kingdom faces pressures due to increasing demand, cost and variable supply. This paper describes immunoglobulin replacement therapy (IGRT) in primary immunodeficiency (PID) and secondary immunodeficiency (SID), providing insight into the growing demand in secondary immune deficiency and to assist in the ongoing planning of UK immunoglobulin provision. A retrospective analysis of the national immunoglobulin database and the UKPID registry was carried out. 3222 PID patients are registered as receiving IGRT. Predominately antibody disorders made up the largest diagnostic category, accounting for 61% of patients. The total cost of IGRT for immunodeficiency for 2015/16 was £40,673,350, equating to an average annual cost of £1,099,254 per centre and £12,124 per PID patient. SCIg accounted for 43.8% and 50.1% of IGRT, with home therapy accounting for 42.7% and 57.5% of place of therapy in the national immunoglobulin database and UKPID registry respectively. In 2015/16 use of Ig in SID increased by 24% over the previous financial year. The overall trends of increasing demand in immunology are mirrored in other specialities, most notably neurology and haematology. These data are the first national overview of IGRT for immunodeficiencies and provide a valuable resource for clinicians and policy makers in the ongoing management of UK immunoglobulin supply.

Keywords

Immunoglobulin, Immunodeficiency, Intravenous, Subcutaneous, England

Abbreviations

UKPID Registry	United Kingdom Primary Immunodeficiency Registry
NID	National Immunoglobulin Database
MDSAS	Medical Data Solutions and Services
IUIS	International Union of Immunological Societies
IGRT	Immunoglobulin replacement therapy
Ig	Immunoglobulin
IVIg	Intravenous Immunoglobulin
SCIg	Subcutaneous Immunoglobulin
PID	Primary Immunodeficiency

Introduction

In 1952 Colonel Ogden Bruton described the first case of X-Linked agammaglobulinaemia (XLA) and treated this young boy with immunoglobulin replacement therapy (IGRT), which had only recently been made available.[1] This case report is often cited as the birth of clinical immunology and since that time immunoglobulin replacement therapy (IGRT) has become the mainstay of treatment for numerous diseases across the primary immunodeficiency (PID) spectrum.[1,2] Over 300 PIDs are now recognised, with approximately 60% associated with hypogammaglobulinaemia.[3] Aside from its use in PID, immunoglobulin therapy also plays a major role in the treatment of secondary immunodeficiencies (SID) following treatment for connective tissue disease (especially with rituximab) and as a manifestation of consequence of treatment of lymphoreticular malignancy and other haematological diseases.[4] In other medical disciplines, most notably neurology a significant amount of immunomodulatory, rather than replacement immunoglobulin is prescribed in the UK.

Since its first description in 1944, production of IGRT has undergone many changes and improvements over the decades.[5] Bruton initially used subcutaneous IGRT, however from 1950 to 1980 IGRT was predominantly administered as an intramuscular (IM) preparation. Changes in the production process allowed IGRT to be given via the intravenous (IV) route in the early 1980s, with the UK switching over to IV preparations in 1982.[6,7] IV preparations are less painful, allowing larger volumes to be administered, leading to higher trough IgG levels and dramatically reducing invasive infection rates, thereby improving survival outcomes.[8,9] Sadly, this period coincided with the emergence of HIV and in addition to Hepatitis C, contaminated products placed a significant burden on cohorts dependent on donor blood products. Whilst there are no confirmed reports of immunoglobulin transmitted HIV, contracting hepatitis C through contaminated immunoglobulin has been confirmed. These iatrogenic infections led to multiple international inquiries and millions of pounds set aside or awarded for compensation.[10] The safety profile of donor immunoglobulin products has since significantly improved with screening of donors and through improvements in the production process with exposure to low pH, pasteurization, detergents and viral filtration.[11] With improved production protocols, these risks of contamination with blood borne viruses have dramatically fallen, although a small theoretical risk still exists, particularly of prion-borne disease.[12,13] The risk of vCJD in the UK has led to the decision that no IGRT is sourced from UK donor pools. To date, no PID patient within the UK has demonstrated clinical evidence of vCJD or abnormal prion protein in tested tissues.[14]

Once the decision has been made to commence IGRT in a patient, the need for continued treatment is kept under review, however it is likely that most will remain on IGRT for the remainder of their life, whether primary or secondary immunodeficiency Patients' clinical outcomes and quality of life are often dependant, sometimes entirely, on their IGRT. The demands made upon the national

immunoglobulin supply from treating immune deficiencies could have significant knock on effects for other specialties for whom a consistent supply of immunoglobulin is also needed. With significant increases in the use of immunoglobulin in immunology, haematology and rheumatology treating secondary antibody deficiency there have been concerns at being able to meet the demands for immunomodulatory treatment, such as ITP (immune thrombocytopenia), CIDP (chronic inflammatory demyelinating polyneuropathy), MMN (multi-focal motor neuropathy). Whilst there may be alternative modalities of treatment for patients undergoing immunomodulation with IVIG, the tolerability, efficacy and therapeutic index of the alternatives do not make them a preferred choice. The NHS therefore needs to ensure a secure and readily available supply of immunoglobulin products to ensure optimal patient outcomes across all licensed indications

These demands place considerable pressure on the procurement and supply of IGRT within the UK. In the early 2000s significant concerns were raised regarding variable supply, increasing demand and high costs of IGRT. In response, the Department of Health produced a review in 2006 which led to the creation of two complementary programs; one based on securing supply and the second, the Demand Management Programme for Immunoglobulin, overseeing the meeting of demand within in the UK.[15] Setting up the Demand Management Programme necessitated the creation of the National Immunoglobulin Database. In a separate initiative, The United Kingdom Primary Immunodeficiency Network (UKPIN) established an online patient registry (UKPID Registry) in 2008.

This study analyses these two national UK databases and aims to describe current practices regarding immunoglobulin therapy in the UK within clinical immunology.

Methods

This study presents data from two UK databases, the UK Primary Immunodeficiency (UKPID) registry and the national immunoglobulin database.

UKPID registry

The UKPID registry collects information from 37 recognised UK immunology centres (covering 97% of UK PID centres).[16] It is the primary registry for PID patients in the UK and offers researchers a single repository of data on UK PID patients.[16] It is also the only national registry to collect data on patients with secondary antibody deficiency. It is funded and overseen by the UK Primary Immunodeficiency network (UKPIN) (http://www.ukpin.org.uk/registry/registry-intro). Anonymised data are collected on individual patients in relation to diagnosis, treatment, investigations, infections and complications. Data entry is cumulative and entries are updated on an annual basis. The development, ongoing management and technical database structure of the registry has been described previously.[16–19] Multicentre Research Ethics (MREC) approval was obtained in 2004 for the ESID

online database (MREC number: 04/MRE07/68). It was subsequently felt that the creation of a standalone UK registry would allow the addition of variables that are of importance and interest to UK clinicians and researchers that may not otherwise be available from the ESID registry, whilst data common to both is shared under appropriate data protection arrangements. Approvals have been amended to reflect the establishment of a UK based database.[16] Data presented is cumulative up until April 2017.

National immunoglobulin database

As part of the newly created Demand Management Programme, the National Immunoglobulin Database was launched in June 2008 (http://igd.mdsas.com). The technical set-up of the database has been described previously.[20] It is managed by medical data solutions and services (MDSAS, http://www.mdsas.com). This database produces a yearly report on IGRT in England and is used extensively by NHS England to support commissioning and therapy initiatives for immunoglobulin. This database is completed prospectively for all immunoglobulin product administration in England. It should therefore provide near complete information on intravenous (IVIg) and subcutaneous (SCIg) usage in England. For the purposes of this study, records were filtered to include immunology use only. Data for the national immunoglobulin database was analysed for the time period April 2013 to April 2016.

Analysis

These two dataset sets were compared to provide enhanced information on the current distribution and management of immune deficiency patients in the UK, with both datasets contributing data for patients receiving their therapy in England and the UKPID registry providing data for patients who received their therapy in England, Wales, Scotland and Northern Ireland. The UKPID registry provided detailed diagnostics and outcome data, with the national immunoglobulin database providing reliable figures on IGRT usage, dosing as well as longitudinal trends.

Variables and results are compared for the two databases. Where only one database source was used, this is clearly stated within the text. Data was also produced for specific centres to provide external comparators and identification of any significant variation in practice. Each centre is anonymised throughout this report, identified by unique ID numbering 1 through to 37.

IGRT usage was broken down by diagnosis, contributing centre, sex and age. Comparisons were made amongst IVIg versus SCIg. Doses and levels are displayed as median and interquartile range (IQR). Where data were only available for a subset of the patients the denominator is stated clearly within the text.

Data were analysed using Microsoft Excel 2016, GraphPad Prism v6.01 (https://www.graphpad.com) and Stata v15.1 (https://www.stata.com).

Results

A total of 2711 patients are recorded as receiving IGRT on the UKPID registry compared to 3222 on the national immunoglobulin database. A breakdown of the patients in the UKPID registry by IUIS category is shown in Supplementary Table 1. Predominately antibody disorders account for 60.9% of patients within the UKPID registry. Demographics of each database by age group and sex are similar (Supplementary Figure a). There is an approximate 50:50 split between male and female in both registries. The proportion of under 18s is 11.4% and 14.5% in the UKPID and National Immunoglobulin Database respectively.

There is a marked variation in the number of patients receiving IGRT amongst immunology centres (Supplementary Figure b), most likely as a result of differing catchment populations The median number of patients receiving IGRT at each centre was 50 (IQR 28-111) for the UKPID registry and 93 (IQR 46-152) for the national immunoglobulin database.

The most common diagnosis in each dataset was CVID accounting for 50% of patients in the UKPID registry and 37.2% of patients in the national immunoglobulin database. Although predominately a PID database, the UKPIN registry does collect information on secondary immunodeficiencies and for both databases, these cases were the second most common diagnosis for patients receiving IGRT (12% - UKPIN, 16.1% National Immunoglobulin Database). Breakdown by diagnosis per the two databases is shown in Table 1. Within the national immunoglobulin database 40.5% of patients are cited as 'Unclassified Hypogammaglobulinaemia. This is due to restrictions in diagnostic classification within this database.

The UKPID database shows a median Ig dose of 579.4 mg/kg/month (IQR 457.1 – 724.1) at a median interval of 3 weeks (IQR 1 – 3) (Figure a). Median IVIg trough level was 9.86mg/dl (IQR 8-11.8). Median random SCIg levels were 9mg/dl (IQR 6.4 – 11.2).

Using the national immunoglobulin database data, the total usage of immunoglobulin for PID in 2015/16 was 1,196,275g, representing 26% of total immunoglobulin use within England. Based on a calculated average cost per gram of £34, this equates to annual cost of £40,673,350. This equates to an average annual cost of £1,099,254 (32,331g) per centre and £12,614 (371g) per PID patient. Secondary antibody deficiencies accounted for 6% (285,392g) of the total immunoglobulin used in 2015/16 making it the fourth commonest diagnosis in the national immunoglobulin database, by volume of immunoglobulin used (the second and third commonest diagnoses being CIDP and MMN respectively). This represents a 24% increase from the previous financial year, 2014/15.

There is marked variation in the ratio of subcutaneous to intravenous therapy amongst centres, mirrored by their variation in preferred place of therapy (home versus hospital) shown in Figure b. Per centre, the median ratio of SC to IV therapy was 1.13 (IGR 0.66 – 1.90) and the median ratio of home to hospital therapy was 1.72 (IQR 1.11 – 3.27). Overall, 43.8% and 50.1% of patients receive their IGRT by the subcutaneous route in the National Immunoglobulin database and UKPID registry respectively. 42.7% and 57.5% of patients receive their therapy at home in the national immunoglobulin and UKPID database respectively (Figure c).

Both databases recorded the most common IVIg preparation as Privigen (26.4% - UKPID, 36.3% - National Immunoglobulin Database). They also both record Hizentra as the most common SCIg prescribed (41.7% - UKPID, 48.3% - National Immunoglobulin Database)

Discussion

Within the national immunoglobulin database, clinical immunology accounts for 35% of all immunoglobulin use, second only to neurology (42%). Primary immunodeficiency, as a group of disorders, accounts for 26% of the 4.6 million grams of immunoglobulin used in 2015-2016.[21] The remaining immunoglobulin therapy used by clinical immunology will be largely related to IGRT in secondary immunodeficiency and as immunomodulation in a range of autoimmune and inflammatory disorders. In the 2015-2016 financial year, the total cost of immunoglobulin use in England was £165 million. It is predicted that by the financial year 2017-2018, the total immunoglobulin cost per annum will be £190 – 200 million.[21] There has been a consistent rise in Ig sales of between 5-10% since the national immunoglobulin database was created. This is in conjunction with a 6.8% reduction in the average price paid per gram between 2011 and 2016 as a result of lower contract prices and product switching.[21] The current national immunoglobulin framework contract supplies seventeen different products through six contracted suppliers.[21]

In June 2017, NHS England made significant changes to immunoglobulin procurement and, in combination with product changes from manufacturers, a significant number of UK patients will have to undergo a change of immunoglobulin product over the coming 12 months. Some changes are as a result of product changes from manufacturers (e.g. Shire's Subcuvia 16% will be replaced with Cuvitru 20%), or some products being withdrawn from the market (e.g. BPL Ltd.'s Vigam 5%). In addition, changes to the national framework agreements have resulted in changes to which products NHS England will procure. Although the two databases have differences in the way they record the brand of immunoglobulin, both agree that Privigen and Hizentra are currently the most common IV and SC preparations prescribed for IGRT in clinical immunology.

UK immunoglobulin has been sourced from plasma donated outside the UK since the vCJD epidemic. Plasma used to fractionate immunoglobulin is sourced from countries that have not had BSE outbreaks and have only background (sporadic) CJD case numbers. The UK is therefore reliant on a global market for the supply of plasma products. The recent shortage of immunoglobulin has been in part due to plasma and plasma products being diverted to more lucrative markets at the same time that limited numbers of plasma donation centres have been opened.

Modern IGRT is available either through the intravenous route (usually on a 3-4 weekly basis) or the subcutaneous route (usually on a weekly basis by pump, but increasingly by rapid push more frequently). Recently, the technique of pre-infusion of SCIg with recombinant human hyaluronidase (facilitated SCIG, fSCIg) may also offer the infusion of SCIG to be extended to 2 to 4 weeks, similar to IVIg.[22] Although, fSCIg is not currently commissioned in England. With adequate training and support either route can be administered at home or hospital. There are various advantages and disadvantages to either route or site of IGRT. The decision to choose one over the other will be individual to each patient, depending on a range of factors including clinical indication, venous access, compliance, patient preference and access to secondary care. It is likely that patients' circumstances will change over the course of their IGRT therapy and site and/or route of IGRT similarly may have to be altered. These results show an almost equal split between IVIg and SCIg amongst the two databases, although home therapy was often preferred in these data with a median ratio of hospital to home therapy of 1.72 per centre. In total, 42.7% and 57.5% of patients received their therapy at home in the national immunoglobulin and UKPID databases respectively. It is worth noting that the recent shortage of immunoglobulin in the UK has exclusively been related to IVIG supply. A progressive switch of patients to subcutaneous immunoglobulin, both for replacement and immunomodulation has the potential to reduce pressure on the demand for IVIG in the UK and has additional advantages in reducing hospital associated costs with IVIG administration to the NHS.[23] The IGRT dosing for all centres appear to fall largely within expected boundaries except for a small number of outliers, possibly due to miscoding of diagnosis and/or speciality. The corresponding median trough level from the UKPID database of 9.86 mg/dl and random IgG trough levels from the SCIg patients of 9mg/dl appear satisfactory and in line with the published literature describing adequate dosing in primary antibody deficiencies.[24] It should be noted that modern practice would dictate individualising IGRT in patients to adequately prevent infections for that individual rather than a blanket target IgG trough level.[25,26]

Comparing Table 1 and Supplementaty Table 2 there are 52 patients within the UKPID registry who have a predominately antibody disorder but are not receving IGRT. There are patients with antibody deficiency who decline IGRT as part of patient choice and are managed with antimicrobial therapy as required or prophylactically.

There are some limitations in this report with some mismatching between the databases as described in this manuscript. This is due to a variety of reasons; differences in the collection time window, variable data entry between database fields, Scotland and Wales not contributing to the National Immunoglobulin Database and differences in grouping some centres together within single trusts. The National Immunoglobulin Database is considered an accurate overview of immunoglobulin use, and is estimated to capture approximately 90% of national immunoglobulin use when compared to data recorded with the Commercial Medicines Unit (CMU).[21] In general, the diagnostic data in the UKPID is of greater quality and accuracy than the National Immunoglobulin Database. Patients with secondary immunodeficiencies contribute a significant proportion of the patients described here (12.0% and 16.1% in the UKPID and National immunoglobulin databases respectively). Their data has been included to demonstrate the significant workload this group contribute to UK clinical immunology and their subsequent demand on the national immunoglobulin supply.

This report is the first comparison and combined analysis of the two major data sources detailing IGRT for immunology within the UK. Allowing for the limitations described above, the data validation between the two datasets shown here, demonstrates their high level of data coverage and detail. These data make a vital contribution to discussions and planning for future immunoglobulin use within the UK. These data provide an accurate overview detailing immunoglobulin use in the UK for clinical immunology both at national and individual centre level. Cost and supply will continue to put pressure on the UK immunoglobulin provision, as well as any future changes in product availability or changes to suppliers. These data, and the demands made by clinical immunology upon the immunoglobulin supply, also have significant implications for other specialities for whom immunoglobulin therapy plays a major role, most notably neurology and haematology. The impact of Brexit may also put additional pressures on supply and careful attention to IGRT supply must be made during the process of exiting Europe. These data here, along with the ongoing data collection by the two databases provides valuable information for clinicians and policy makers in helping to ensure reliable and adequate supply of immunoglobulin products for PID patients within the UK.

Table of Figures

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Tables

Table 1 Breakdown of diagnosis for those receiving IGRT according to each database

Diagnosis	**UKPID Registry**	**National Immunoglobulin Database**
CVID	1358 (50.1%)	1199 (37.2%)
Secondary Immunodeficiency	326 (12.0%)	519 (16.1%)
XLA	198 (7.3%)	N/A
SPAD	121 (4.5%)	132 (4.1%)
Unclassified hypogammaglobulinaemia	197 (7.3%)	1306 (40.5%)
Thymoma with ID	68 (2.5%)	17 (0.5%)
IgG subclass	44 (1.6%)	N/A
HIGM	41 (1.5%)	36 (1.1%)
Post HSCT	0 (0%)	13 (0.4%)
IgA deficiency	13 (0.5%)	N/A
IgA & IgG subclass deficiency	10 (0.4%)	N/A
Total	2711	3222

CVID = Common Variable Immunodeficiency; ID = Immunodeficiency; HIGM = Hyper IgM; HSCT = Haematopoietic Stem Cell Transplantation; XLA = X-Linked Agammaglobulinaemia; SPAD = Specific IgG Deficiency

Supplementary Table 1 Current breakdown of patients in the UKPID registry by IUIS category

IUIS PID category	**Numbers**
Predominantly antibody disorders	2763
Complement deficiencies	575
Other well defined PIDs	333
Predominantly T-cell deficiencies	320
Phagocytic disorders	177
Unclassified Immunodeficiencies	187
Autoimmune and immune dysregulation syndromes	94
Defects in innate immunity	38
Auto inflammatory syndromes	27
Missing diagnosis	26
Total	**4540**