

Unraveling the Mystery of Polyvalent Immunoglobulins in Belgium: Do We Have an Indication?

Christophe de Meester Jolyce Bourgeois Stephan Devriese
Lorena San Miguel

Belgian Health Care Knowledge Center (KCE), Brussels, Belgium

Keywords

Immunoglobulins · Intravenous infusions · Subcutaneous · Medicine/therapeutic use

Abstract

Introduction: Worldwide, polyvalent immunoglobulin (Ig) use is rising. Together with the limited supply, this puts pressure on Ig availability. A clear overview on a country's usage pattern helps in forecasting future needs. This research aims to provide an overview of Ig use in Belgium on the different indications, including an estimation of off-label use. **Methods:** Multiple data sources were used. Existing claims data were explored for reimbursed Ig use between 2010 and 2018. General 2018 sales data from the firms were compared to the reimbursed use to serve as a proxy for off-label use. Indication-specific information was retrieved via a proxy: diagnostic codes available during day-care and inpatient hospitalization. **Results:** In 2018, 7,556 patients had reimbursed Ig. The most prevalent indication, both in terms of patient numbers and volume, was primary immunodeficiency (PID). In Belgian hospitals, the currently reimbursed indications represented 84.4% of patients (PID [≈35%], secondary immunodeficiency [SID] [≈21%], primary immune thrombocytopenia [≈10%], chronic inflammatory demyelinating neu-

ropathy [CIDP] [≈8%], Guillain-Barre syndrome [≈6%], Kawasaki [≈2%], streptococcal toxic shock [≈2%] and multiple motor neuropathy [≈1%]), and 82.4% of Ig use (predominantly PID [≈33%] and CIDP [≈21%]). Although no direct data on off-label use were available, crude estimates derived from indirect sources showed a proportion of around 15.4%. **Conclusion:** Our research offers the first comprehensive overview on Ig use in Belgium, including a detailed description of reimbursed use, as well as approximations to off-label use. In view of increasing pressure on Ig availability, better understanding Ig needs and trends, would benefit from an effective indication-specific national registry system (ideally covering both reimbursed and nonreimbursed use).

© 2021 S. Karger AG, Basel

Introduction

Immunoglobulins (Ig), also called antibodies, naturally circulate in the human blood. Once purified from blood plasma of healthy humans, Ig can also be used as a drug therapy. Igs were initially used as replacement therapy for

Edited by: H.-U. Simon, Bern.

patients with immune defects, who cannot adequately produce Ig to combat infection (agammaglobulinemia/hypogammaglobulinemia) [1]. Since the 1980's, Igs are increasingly linked to anti-inflammatory and immunomodulating properties, and as a result, they slowly became an important treatment option in a number of (often rare) inflammatory and autoimmune diseases (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy) [2]. The exact working mechanism of Ig is not fully elucidated and therapeutic areas where they are tested are scattered over hematology, neurology, dermatology, oncology, rheumatology, and pediatrics. Although literature shows that evidence from high-quality randomized controlled trials remains limited, the list of possible indications keeps growing [3, 4].

Ig's are licensed for a limited list of indications (often 6 to 9 depending on the country). However, off-label use is not uncommon and appears to be accepted for some, often very rare indications [5, 6].

In Belgium, products for intravenous administration (IVIg) are licensed for the following 8 indications: primary immunodeficiency (PID) with impaired antibody production, secondary immunodeficiency (SID) due to hematological diseases or stem cell transplantation, chronic inflammatory demyelinating neuropathy (CIDP), primary immune thrombocytopenia (PIT), Kawasaki disease, multiple motor neuropathy, Guillain-Barre syndrome, and streptococcal toxic shock. Subcutaneous administration (SCIg), most often intended as chronic at-home treatment, is limited to PID, SID, and stabilized CIDP patients.

The growing list of potential indications, the limited evidence, the increasing use, and associated cost, together with the limited supply have incited countries to launch initiatives encouraging appropriate use of Ig (e.g., guidelines or national authorization systems) [5, 6]. Despite the aforementioned initiatives, publicly available data on usage remains limited. Therefore, the aim of this study is to offer a detailed comprehensive overview and understanding of Ig use in Belgium, by describing indication-specific Ig consumption.

Materials and Methods

No single data set containing all relevant information on Ig use exists to this date in Belgium. Therefore, multiple data sources were consulted in order to offer a more complete picture, most of which only covered reimbursed Ig use. Given the lack of registration for indications, diagnostic codes available in day-care or inpatient hospitalization were used as proxy for these (see further).

In all data sources, the selection criteria to retrieve Ig use were based on ATC codes [7] J06BA01 (Subcutaneous Ig/SCIg) or J06BA02 (Intravenous Ig/IVIg). More details about the databases used are available in the online suppl. data; for all online suppl. material, see www.karger.com/doi/10.1159/000516951.

Annual Public Expenditure and Reimbursed Ig Consumption (Health-care reimbursement data consulted):

Intermutualistisch Agentschap – Agence Intermutualiste (IMA – AIM) performed our preprogrammed analysis on annual public expenditure and volume of reimbursed Ig (i.e., products and doses), both for the hospital and ambulatory settings over the period 2010–2018. The volume of Ig reimbursed via unmet-medical need programs is not captured via this source of data.

Sales Data

Data on overall sales of Ig (IVIg and SCIg) in Belgium in the year 2018 were obtained from the Belgian Federal Agency for Medicines and Health Products, and pharmaceutical firms holding a market authorization for the products available on the Belgian market. These data offered an indication of the total size of the Belgian market, not limited to reimbursed use.

Indication-Specific Data

In the hospital setting, diagnostic codes are available via the TCT database and were used as a proxy for the indication. A list of potentially interesting indications for Ig use in Belgium was drafted based on a literature review [3] and expert opinion. For the 8 reimbursed indications as well as 11 off-label indications, the corresponding ICD-10 codes [8] were identified (for further details see online suppl. data).

A cross-match between the listed indications and the diagnostic codes available in the TCT data was performed. The following procedure to attribute one indication to each patient was pursued:

1. When one of the selected diagnostic codes (listed in the online suppl. data) matched a registered diagnosis in the TCT, this diagnosis was retained as the proxy indication.
2. When multiple diagnosis codes were identified, the proxy indication was selected based on epidemiological data (which diagnosis is most prevalent) and input of experts.
3. When no preselected diagnostic code was found in the registered diagnosis in TCT, this was labeled “other indications.”

Stays for which no diagnostic code was registered were excluded from the per proxy indication analysis. However, extrapolations based on the available data were made in order to estimate the total use in hospital.

In the ambulatory setting, only PID and SID were reimbursed in 2018. However, only a global estimate covering both was available in the consulted data sets, and therefore, no exact indication-specific proportions could be used in our analysis.

Estimation of Off-Label Use

To be able to estimate the total amount of off-label use in Belgium, it was necessary to take into account the off-label use in both hospitals and community. For that purpose, sales figures were compared to reimbursed Ig use data for the year 2018. Possible differences may offer an approximation to the volume of “non-reimbursed” use, which was used as a proxy measure for off-label use.

It is important to highlight that nonreimbursed use does not equal off-label use, as there are certain circumstances under which

Ig use for a “licensed” indication may not be reimbursed (e.g., patients not covered by the Belgian national health insurance). Included in the “non-reimbursed use” there is also some off-label use funded via the unmet-medical needs programs or the special solidarity funds. A crude calculation, based on the overall expenditure for Ig funded via these mechanisms, and taking into consideration the price per gram in 2018 was used to estimate the volume. More detail about the methodology can be found in KCE report 336 [9].

Results

Total Ig Consumption in Belgium

The total sales of IVIg and SCIg in Belgium were 2,132.9 kg in 2018 (shown in Fig. 1). In the same year, the total reimbursed volume of Ig was 2,010.3 kg, of which 1,751.4 kg represented IVIg delivered by hospital pharmacies, and 258.9 kg were SCIg (12.4 kg distributed by hospital pharmacies and 246.5 kg by community pharmacies). The total number of patients with reimbursed Ig in 2018 was 7,556.

According to these figures, the proportion of nonreimbursed use could amount to a maximum of 5.7% (122.6 kg) in 2018. In the hospital setting, this was 2.1% (37.6 kg), while in the ambulatory setting this was 25.6% (85 kg).

Evolution of Reimbursed Use in Belgium

The overall reimbursed consumption of Ig rose from around 1,126 kg in 2010 to 2,010 kg in 2018, coinciding with a national budget rise from around 50 million euro in 2010 to 90 million euro in 2018. There was a steady increase over that time period, with the exception of a stable consumption between the years 2013 and 2014, and between 2016 and 2017 (shown in Fig. 2). The overall mean increase in consumption of Ig for reimbursed indications appears to be around 5.5% per year, with a growth of 0.7 and 6.1% in the last 2 years for which data were available. The growth is more predominant for SCIg dispensed via the ambulatory setting (community pharmacy). IVIg is reserved for administration in the hospital setting due to the need for specific medical material and staff and appears to be mainly administered in the day-care hospital setting (>70% of all hospital administrations), for which sometimes, consecutive days of administration are necessary to obtain the prescribed dose.

Indications of Reimbursed Ig

Proxy indications of Ig use are only available for the hospital setting. In 2018, the TCT data included 6,758 patients and 1,756 kg of Ig. In a number of cases, determined by the registration rules, a diagnosis was not recorded,

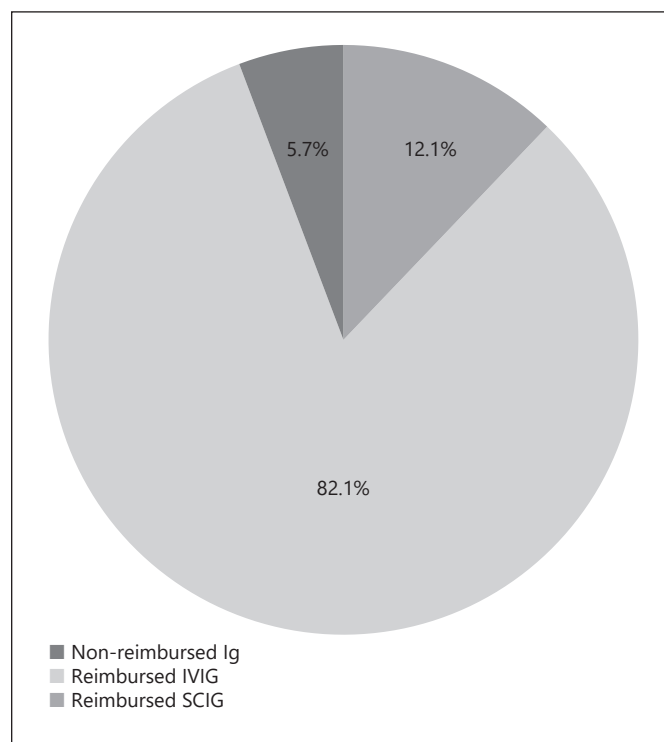


Fig. 1. Ig consumption in Belgium in 2018 (source IMA-AIM, IV: intravenous, SC: subcutaneous). Ig, immunoglobulin; IMA-AIM, Intermutualistisch Agentschap – Agence Intermutualiste.

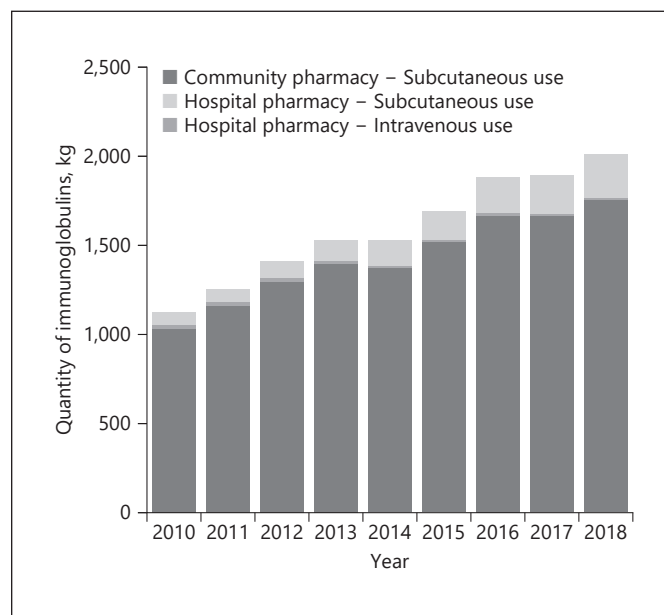


Fig. 2. Evolution of reimbursed Ig uses in Belgium per type of administration and setting (source: IMA-AIM). Ig, immunoglobulin; IMA-AIM, Intermutualistisch Agentschap – Agence Intermutualiste.

Table 1. Indication of reimbursed Ig

Indication	Analysis population		Extrapolation to entire population	
	patients, n (%)	quantity of Ig, kg, n (%)	patients, n (%)	quantity of Ig, kg, n (%)
Hospital setting (source = TCT)				
Official reimbursed indications in Belgium	4,624 (84.4)	957.6 (88.3)	5,703 (84.4)	1,549.5 (88.3)
PID – Hospital	1,911 (34.9)	355.4 (32.8)	2,357 (34.9)	575.2 (32.8)
SID – Hospital				
Multiple myeloma	407 (7.4)	65.0 (6.0)	502 (7.4)	105.1 (6.0)
Chronic lymphocytic leukemia	217 (4.0)	40.7 (3.8)	268 (4.0)	65.9 (3.8)
Other	524 (9.6)	82.1 (7.6)	646 (9.6)	132.8 (7.6)
PIT	533 (9.7)	86.1 (7.9)	657 (9.7)	139.4 (7.9)
CIDP	452 (8.2)	227.7 (21.0)	558 (8.2)	368.4 (21.0)
GBS	309 (5.6)	55.0 (5.1)	381 (5.6)	89 (5.1)
Kawasaki disease	103 (1.9)	4.1 (0.4)	127 (1.9)	6.6 (0.4)
MMN	57 (1.0)	30.4 (2.8)	70 (1.0)	49.2 (2.8)
Streptococcus toxic shock syndrome	111 (2.0)	11.1 (1.0)	137 (2.0)	17.9 (1.0)
Off-label indications commonly reimbursed in other countries*	74 (1.4)	10.0 (0.9)	91 (1.4)	16.1 (0.9)
Solid organ transplant rejection	29 (0.5)	5.7 (0.5)	36 (0.5)	9.3 (0.5)
Hemolytic disease in newborns	13 (0.2)	0.1 (0.0)	16 (0.2)	0.1 (0.0)
Myasthenia gravis	8 (0.1)	1.6 (0.1)	10 (0.1)	2.5 (0.1)
FNAIT	8 (0.1)	0.1 (0.0)	10 (0.1)	0.1 (0.0)
Von Willebrand's disease	<5	0.3 (0.0)	<5	0.4 (0.0)
Inflammatory myopathies	6 (0.1)	1.2 (0.1)	7 (0.1)	1.9 (0.1)
Stiff-person syndrome	<5	0.4 (0.0)	<5	0.6 (0.0)
Pure red cell aplasia (Erythroblastopenia)	0	0	0	0
Pemphigus (vulgaris-foliculae)-immunobullous disease	0	0	0	0
Post-transfusion purpura	0	0	0	0
Antibody-mediated types of encephalitis	7 (0.1)	0.7 (0.1)	9 (0.1)	1.2 (0.1)
Other indications**	781 (14.3)	117.3 (10.8)	963 (14.3)	189.8 (10.8)
Total hospital setting	5,479	1,084.9	6,758	1,755.5
Ambulatory setting (source = IMA – AIM)				
PID – SID [#]	1,118	246.5	1,118	246.5
Total ^{##}	–	–	7,876	2,002.0

Source: TCT; PID, primary immunodeficiency; SID, secondary immunodeficiency; PIT, primary immune thrombocytopenia; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barre syndrome; MMN, multifocal motor neuropathy; Ig, immunoglobulin; SCIG, subcutaneous administration; IMA-AIM, Intermutualistisch Agentschap – Agence Intermutualiste. * Countries considered included “Australia, Canada, England and France.” These were selected given their recent activities in reviewing this field. ** Other indications are ICD-10 codes that were not identified in the potentially interesting indications, that is, the 8 reimbursed + the 11 off-label but commonly reimbursed and recognized in other countries. [#] In ambulatory setting, Ig reimbursement is limited to SCIG, for either PID or SID. No extrapolation is needed. ^{##} Small differences in terms of total number of patients and total reimbursed volume of Ig are observed when comparing the source of indication-specific data here used (TCT database) and the global data presented in the IMA – AIM database. Some patients may have also used Ig in both the hospital and ambulatory settings.

reducing the dataset to 5,479 patients, and 1,085 kg of Ig. Approximately, 81% of the patients and 62% of the reimbursed Ig volume were retained for the analysis on indications. Table 1 summarizes the results of this analysis.

Ig use for which an officially reimbursed indication was found was present in 4,624 (84.4%) patients, and the use in an off-label indication in 74 (1.4%) patients. For 781 (14.3%) patients, no previously selected Ig indication

was identified (see “other indications” in Table 1). The ICD codes of these patients were mainly diagnosis of neoplasms, hematological diseases, and certain disorders involving immune mechanism, as well as diseases of the nervous system.

Five main indications appear to account for the large majority of the Belgian patients receiving Ig in the hospital setting: PID (≈35% of patients), SID (≈21% of patients),

primary immune thrombocytopenia ($\approx 10\%$ of patients), CIDP ($\approx 8\%$ of patients), and Guillain-Barre syndrome ($\approx 6\%$ of patients). There are 378 of the PID patients (19.8% of the total PID patients) who had also a SID diagnosis. These patients were categorized as PID patients for the purpose of our analysis (see Materials and Methods).

In the hospital, in terms of quantity, the 8 official reimbursed indications represented 88.3% of the total volume, with PID ($\approx 33\%$), CIDP ($\approx 21\%$), and SID ($\approx 17\%$) representing the largest volumes. It is important to highlight that the overall volume of PID and SID is higher than the 50% reported in the hospital setting, given that reimbursement in the ambulatory setting for these 2 indications is also possible, which would increase the overall proportion of PID and SID use to 56.2%.

Off-Label Use

When sales data and information on actual reimbursed Ig use were compared (all settings and types of administrations considered), there was an overall difference of 122.6 kg in 2018, representing the nonreimbursed use in both the hospital and ambulatory sector. Included in the 122.6 kg “non-reimbursed use” there is 7.1 kg funded via the unmet-medical need programs.

The indication-specific analysis for the hospital setting previously described also showed 74 patients with off-label indications that were treated with reimbursed Ig (11 kg) in 2018. Moreover, there was a considerable group of patients ($n = 781$), representing 117.3 kg, for which no preselected diagnosis was found, and could therefore, also represent “off-label” use. Since the indication-specific analysis could only be performed for 62% of the total Ig consumed in hospitals, extrapolations would indicate that “reimbursed” off-label use could be around 206 kg (≈ 16.1 kg for the 11 indications and ≈ 189.8 kg for those without a selected indication) in the hospital setting.

Adding up the estimates from the nonreimbursed use (difference between sales and reimbursed use), and the “reimbursed” off-label use identified via the indication-specific analysis for the hospital setting, the off-label use in Belgium in the year 2018 would have been of around 15.4%. However, careful interpretation is warranted since this is merely based on proxies.

Discussion/Conclusion

This research is the first providing an overview of the Ig market in Belgium for both the hospital and the ambulatory settings, including an indication-specific analysis,

as well as an estimation of off-label use. To our knowledge, there is no readily available national overview of off-label use. Either one must analyze the limited available country-specific annual reports (i.e., available for England and Australia) or rely on data samples (data from some hospitals or regions). These Belgian data and methodology can serve as an example for other researchers trying to get an overview of their national usage patterns, which could in turn serve as a basis for forecasting future needs.

Growing Use in a Tight Market

In Belgium, the annual growth rates over the period 2010–2018 ranged between 6 and 12%, with the only exception of 2 time periods in which consumption remained practically stable: 2014 and 2017. This was probably due to the more stringent reimbursement criteria (e.g., involvement of specific experts for diagnosing), introduced in those 2 years.

Similar growth rates are seen in other countries such as England, Canada, and Australia [10–13]. Key drivers for this growth include an aging population, improved diagnostic possibilities (e.g., via innovations such as next-generation sequencing) and the recognition and adoption of Ig as a valuable treatment for several immunological and neurological diseases, including some off-label indications [14, 15].

As in other countries, the largest growth rates are seen in SCIg use in ambulatory care, which fits in the health-care trend of treating patients close to (or at) their homes, especially for chronic diseases. However, intravenous infusions represent the most frequent type of administration and are expected to maintain their dominance in the future. In Belgium, SCIg use has experienced a steady growth from 2012, but still represents a small part of the total consumption of Ig in Belgium (13% in 2018). This may be explained by the reimbursement status of SCIg in this country, which until recently was limited to 2 indications: PID and some forms of SID. However, since September 2020, one SCIg product (i.e., Hizentra[®]) is also reimbursed for use in stabilized CIDP patients and will enforce this growth, as important dosages are used in CIDP patients.

Capturing Indication-Specific Data

Currently in Belgium, there is no central overview on the indications for which Ig are used, though they are strictly regulated via explicit reimbursement criteria for 8 indication groups. Evidence that patients meet these indication-specific criteria as well as a justification for

their use must be documented at the hospital level (for IVIg) or health insurance (for SCIG) but is not always electronically/easily available and is not captured nationally. However, the tight market and the increasing risk of supply problems make it necessary to be able to forecast Ig needs and to detect trends in usage. In this research, indirect ways needed to be applied to estimate the use per indication.

It is important to highlight that the indication-specific analysis represents only the reimbursed (publicly funded) part of Ig hospital consumption in Belgium. A peculiarity was that for around 11.7% of the reimbursed Ig use in the hospitals, no official reimbursed (licensed) indication could be linked. A small proportion could be linked to recognized off-label indications (such as hemolytic disease in newborns, myasthenia gravis...), but the majority was linked to diagnostic codes related to neoplasms, hematological diseases, and certain disorders involving the immune mechanism. Whether these reflect errors, incompleteness in coding/registration, or use in off-label indications could not be elucidated.

Among the licensed indications, PID and CIDP were the most prevalent, with respectively 33 and 21% of the volume. These figures are not far from those reported in England's annual report for the same year (i.e., 2018/2019), with PID accounting for 26% and CIDP for 21% of the overall volume. However, an Australian report shows that SID was the medical condition for which the greatest proportion of Ig was used in 2017–2018 (27%), closely followed by CIDP (21%). In our analysis, around 20% of the PID patients had also a SID diagnosis (but to simplify the analysis and facilitate interpretation, these were categorized as PID patients). Discerning adult PID from SID can be challenging (e.g., symptoms may appear at an advanced age, and the role of genetics is not well defined) [16]. These difficulties, coupled with the complex reimbursement criteria, may have produced inconsistent diagnostic coding. Therefore, an underrepresentation of SID in our analysis cannot be excluded.

Off-Label Use

Several countries have guidelines which include off-label indications [5, 6]. Nevertheless, data on volume off-label use remains scarce. A French study, limited to hospitalized patients in Ile de France region, reported off-label use in approximately 30% of patients. In England, an analysis of the annual report shows that around 20% of patients receive Ig treatment for off-label indications [12, 13, 17].

In Belgium, off-label use is publicly funded only via specific unmet-medical need programs, and this volume is not included in the dataset of reimbursed medicines (IMA-AIM). However, a crude calculation based on annual remuneration of Ig via unmet-medical need programs indicates that this is very limited. A comparison between Ig sales on the Belgian market on the one hand and reimbursed Ig use on the other could give an estimation on the total volume of nonreimbursed use, which in turn can serve as a proxy for off-label use. It is important to note that sales do not equal usage. The difference of 122.6 kg may also include stocking volumes and/or (parallel) exports. Moreover, the indication-specific analysis in the hospital setting showed that there might be a considerable amount of reimbursed off-label use (around 200 kg). This amount should also be interpreted with caution, as this volume is based on diagnostic codes registered in the database, so incomplete registration or registration errors could also be responsible for at least a part of these 200 kg.

Given all aforementioned uncertainties, the 15.4% off-label use should be taken as an approximation. A Belgian study in the hospital setting linked off-label use to around 40–50% of all Ig patients in the year 2007, although its methodological limitations, recognized by the author, may have resulted in an overestimation [18].

Limited Supply

Because of its status as a costly and scarce medicine, all current recommendations and reimbursement criteria highlight the need for careful consideration before starting Ig in a patient (severity of the disease, approval/confirmation of diagnosis by experts, ...), and regular reassessment, including the consideration to wean off patients from Ig (e.g., CIDP) [6, 19–21]. Moreover, while Ig use is growing worldwide, more and more supply problems arise [22, 23]. The reasons are not unique and are due to factors such as a limited supply of plasma, a complex and time-consuming production, contracts based on forecasting or manufacturers allocating their products to specific countries according to the price obtained in that market (the product follows the price) [24]. Currently, the COVID-19 crisis is affecting plasma collection, mainly in the USA, which is the dominant exporting country. This puts extra pressure on an already strained system [25, 26]. As a result, shortages have been notified in Belgium, where all products have the status “critically unavailable” since November 2020, likely to continue until June 2021 [27].

It is recommended to have a more controlled system for Ig use, capturing both licensed and off-label indications. Already in 2008, the National Health Service in England invested in a national Ig database (<http://igd.mdsas.com/ig-database/>) [13], and more recently, since 2018, Australia also has a nationwide online system (i.e., BloodSTAR) to manage access to government-funded Ig [28]. These indication-specific data registration systems, coupled with annual reports, enable them, to not only better understand changes in use and evolutions, but also respond quickly to potential supply shortages. In time of shortages, direct actions may be needed in order to distribute the scarce resources on the best and most fair way, such as prioritize as temporarily the most severe indications for which no alternative treatments exist, or lowering doses in indications in which this may be an option. These approaches have already been implemented in France and England [6, 19–21].

Limitations

There are some important limitations that should be recognized. First of all, the diagnostic codes are proxies for indications, as these are related to the reason of hospital stay, and the indication for Ig as such is not captured in the data. Not every Ig indication could be linked to a specific ICD code. Often a grouping of several ICD codes had to be used to approximate the Ig indication as much as possible. Moreover, only 62% of the hospital volume, consumed in >99% of inpatient stays and 56% of day-care stays (for a total of 81% of patients), could be linked to diagnostic codes, either because coding was missing during the coupling or because the specificity of the hospital stay did not require a diagnostic code (i.e., psychiatric or emergency admissions or some day-care hospitalizations). When extrapolations were used to estimate the total volume of Ig by indications in the hospitals, the same proportions were used, and these were not taking into account the relative dominance of discarded day-care stays, for which maybe more or less chronic or off-label indications were possible. Moreover, in case of patients with >1 diagnosis, assumptions were made to link the patient to only one indication, but whether our assumptions reflect or not the real indication for which Ig was prescribed cannot be assured. The limitations and uncertainties regarding the results here listed should serve as an additional motivation to implement central registration and monitor indication-specific use (ideally for both reimbursed and non-reimbursed) at a national level.

Conclusion

In view of increasing pressure on Ig availability, a better understanding of Ig needs and trends is needed. Ultimately, an effective indication-specific national registry system (covering both reimbursed and nonreimbursed use) would provide the most valuable tool to facilitate rapid and informed decision-making in this complex field. However, the planning and implementation of such a system is not an easy task. In the meantime, our research offers the first comprehensive overview on Ig use in Belgium, including a detailed description of reimbursed use, as well as approximations to off-label use at a national level.

Acknowledgements

We kindly thank the Federal Agency for Medicines and Health Products, as well as the pharmaceutical companies for providing the sales data. We kindly thank the IMA – AIM which performed our preprogrammed analysis on annual public expenditure database. As this work was part of a research of the Belgian Health-Care Knowledge Centre (KCE Report 336A), we would like to thank all experts involved in this research.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent from participants was not required in accordance with local/national guidelines. This article does not contain any studies involving human participants performed by any of the authors. All databases consulted are anonymous data, which are not subject to the Belgian privacy law. The Belgian Health-Care Knowledge Center (KCE) has a direct access to the TCT data, regulated by law.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors. It was supported by the government-approved work program of the Belgian Health-Care Knowledge Center (KCE).

Author Contributions

Author Christophe De Meester: contributed to conception, design, data acquisition, performed all analyses, data interpretation, drafted, and critically revised the manuscript. Author Jolyce Bourgeois: contributed to conception, design, data acquisition, inter-

pretation, drafted, and critically revised the manuscript. Author Stephan Devriese: contributed to conception, design, data acquisition and analysis, interpretation, and critically revised the manuscript. Author Lorena San Miguel: contributed to conception, design, data analysis, interpretation, and critically revised the manuscript.

References

- Bruton OC. Agammaglobulinemia. *Pediatrics*. 1952 Jun;9(6):722–8.
- Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981 Jun 6;1(8232):1228–31.
- Bourgeois J, Fairon N, San Miguel L. Polyvalent immunoglobulins – Part 1: a rapid review. health technology assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2020.
- Garraud O. Injectable immunoglobulins, immunodeficiency and off-label clinical trials, source plasma and ethical concerns and debates. *Transfus Apher Sci*. 2019 Aug;58(4):529–30.
- National Blood Authority Australia. *Criteria for the clinical use of immunoglobulin in Australia (the Criteria)*; 2021.
- NHS England. *Updated Commissioning Criteria for the use of therapeutic Immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England*; 2019.
- WHO Collaborating Centre for Drug Statistics Methodology GfAcaDa. *WHO Collaborating centre for drug statistics methodology*; 2021.
- SPF Santé Publique SdlCAeE. *Manuel de codage ICD-10-BE*; 2019.
- de Meester C, Bourgeois J, Devriese S, San Miguel L. Polyvalent immunoglobulins – Part 2: Use in Belgium. *Health Technology Assessment (HTA)*. Brussel: Belgian Health Care Knowledge Centre (KCE); 2020.
- Canadian Blood Services. *Immune Globulin 5 year trend in grams: intravenous and subcutaneous*; 2020 [cited 2020 May 29]. Available from: https://blood.ca/sites/default/files/Immune_Globulin_5_Year_Trend_by_Grams_2018_2019.pdf.
- National Blood Authority Australia. *Annual report: issues of immunoglobulin products, 2014–15 to 2018–19*; 2020 [cited 2020 May 29]. Available from: <https://www.blood.gov.au/pubs/1819report/part-2-annual-performance/objective-1-secure-supply-blood-and-blood-products.html>.
- NHS England. *Immunoglobulin database: annual report 2017/2018*; 2018.
- NHS England. *Immunoglobulin database: annual report 2018/19*; 2019.
- Allied Market Research. *Intravenous immunoglobulin market overview*; 2019 [cited 2020 Jun 18]. Available from: <https://www.allied-marketresearch.com/intravenous-immunoglobulin-IVIG-market>.
- Market Research Bureau. *Plasma supply into the future. workshop on plasma collection – European blood alliance and international plasma and fractionation association*. Amsterdam; 2020.
- Thaventhiran JED, Lango Allen H, Burren OS, Rae W, Greene D, Staples E, et al. Whole-genome sequencing of a sporadic primary immunodeficiency cohort. *Nature*. 2020 Jul;583(7814):90–5.
- L'Observatoire des médicaments ddmedlitO. *Immunoglobulines humaines normales intraveineuses et sous-cutanées: bilan des utilisations dans les établissements de santé d. Ile-de-France*; 2017.
- Simoens S. The use of intravenous immunoglobulins in Belgium. *Int Arch Allergy Immunol*. 2011;154(2):173–6.
- L'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). *Hiérarchisation des indications des immunoglobulines humaines polyvalentes France*. ANSM; 2019.
- Ontario Regional Blood Coordinating Network (ORBCON). *Ontario immune globulin management guidelines version 4*; 2018.
- Adrichem ME, Eftimov F, van Schaik IN. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy, a time to start and a time to stop. *J Peripher Nerv Syst*. 2016 Sep;21(3):121–7.IN.
- Food and Drug Administration. *Information about immune globulin (Human) product shortage*; 2019 [cited 2020 Jun 8]. Available from: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-about-immune-globulin-human-product-shortage>.
- Hartmann J, Klein HG. Supply and demand for plasma-derived medicinal products: a critical reassessment amid the COVID-19 pandemic. *Transfusion*. 2020 Nov;60(11):2748–52.
- Farrugia A, Grazzini G, Quinti I, Candura F, Profili S, Liunbruno GM. The growing importance of achieving national self-sufficiency in immunoglobulin in Italy. The emergence of a national imperative. *Blood Transfus*. 2019 Nov;17(6):449–58.
- de santé (ANSM). *L'Agence nationale de sécurité du médicament et des produitsTensions d'approvisionnements du marché français en immunoglobulines humaines-COVID19*; 2020.
- Plasma Protein Therapeutics Association. *Risks Decreasing European Plasma Collection*; 2020. Available from: <https://www.ppta-global.org/media-and-information/press-releases/1075-new-edition-of-edqm-blood-guide-risks-decreasing-european-plasma-collection>.
- Federal Agency for Medicines and Health Products. *Pharmastatus*. [cited March 2, 2021]; Available from: <https://pharmastatus.be/>
- National Blood Authority Australia. *National immunoglobulin governance program*; 2019 [cited 2019 Mar 20]; Available from: <https://www.blood.gov.au/ig-program>.

Supplementary data

Unravelling the mystery of Polyvalent Immunoglobulins in Belgium: do we have an indication?

Databases

Healthcare reimbursement data: In Belgium, residents, must in principle, have a compulsory health insurance provided through one of the seven national sickness funds and funded by social security contributions and general taxation. Healthcare reimbursement data from claims are available at IMA – AIM (Intermutualistisch Agentschap – Agence Intermutualiste), which is a non-profit organisation that manages and analyses information on all reimbursements related to the compulsory health insurance, collected by the Belgian sickness funds. These data cover all ambulatory and in hospital services (consultations, pharmaceuticals, diagnostic and therapeutic procedures), and some patient socio-demographic and socio-economic characteristics.

TCT database: In Belgium, all general hospitals are required to submit twice a year a large set of data on all inpatient and day-care hospital stays and emergency room contacts, including diagnostic information to the Federal Public Service (FPS) for Health, Food Chain Safety and Environment: the Minimal Hospital Data. These are linked by a separate cell to claims data from the Sickness Funds to become the TCT data set

More details on databases and on methodology are available at

[https://kce.fgov.be/sites/default/files/atoms/files/KCE 336 Immunoglobulins Part%202 use in Belgium Report 0.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_336_Immunoglobulins_Part%202_use_in_Belgium_Report_0.pdf)

Table S1: ICD-10-BE procedure and diagnostic codes used to identify the relevant selected Ig indications in Belgium

Indication	ICD-10-BE	Details
Official reimbursed indications in Belgium		
1. Primary Immunodeficiency (PID)	D80	Immunodeficiency with predominantly antibody defects
	D81	Combined immunodeficiencies
	D82	Immunodeficiency associated with other major defects
	D83	Common variable immunodeficiency
	D84	Other immunodeficiencies
2. Secondary Immunodeficiency (SID): -Multiple Myeloma (Kahler's disease) -Chronic Lymphatic leukaemia - B cell malignancies with Bcell depletion due to chemo or monoclonal antibodies	C900	Multiple myeloma
	C911	Chronic lymphocytic leukaemia of B-cell type
	T860	Complications of bone marrow transplant
	T865	Complications of stem cell transplant
	Z9484	Stem cells transplant status
	Z9481	Bone marrow transplant status

-(Allogenic) stem cell transplantation/ hematopoietic stem cell transplantation	T8603	Bone marrow transplant infection
	C81	Hodgkin lymphoma
	C82	follicular lymphoma
	C83	Non-follicular lymphoma
	C85	Other specified and unspecified types of non-Hodgkin lymphoma
	C88	Malignant immunoproliferative diseases and certain other B-cell lymphomas
	C901	malignant plasma cell neoplasms
	C902	Extramedullary plasmacytoma
	C903	Solitary plasmacytoma
	C910	Acute lymphoblastic leukaemia
	C913	Prolymphocytic leukaemia of B-cell type
	C914	Hairy cell leukaemia
	C919	Lymphoid leukaemia, unspecified
3. Primary immune thrombocytopenia (PIT)	D693	Immune thrombocytopenic purpura
4. Chronic inflammatory demyelinating polyneuritis (CIDP)	G6181	Chronic inflammatory demyelinating polyneuritis
5. Guillain-Barré Syndrome (GBS)	G610	Guillain-Barre syndrome
6. Kawasaki Disease	M303	Mucocutaneous lymph node syndrome [Kawasaki]
7. Multifocal Motor Neuropathy (MMN)	G6182	Multifocal motor neuropathy
8. Streptococcus toxic shock syndrome	A483 (+B950, +B951, +B952, +B953, +B954, +B955)	Toxic shock syndrome (+Streptococcus, and Enterococcus as the cause of diseases classified elsewhere)
	A40	Streptococcal sepsis
	A41	Other sepsis
	P36	Bacterial sepsis of newborn
Off-label Indications commonly reimbursed in other countries*		
9. Solid Organ transplant complications	T86	Complications of transplanted organs and tissue
	D8981	graft-versus-host disease
10. Haemolytic disease in newborns	P55	Haemolytic disease of newborn
11. Myasthenia gravis	G700	Myasthenia gravis
	G708	Other specified myoneural disorders
	G731	Lambert-Eaton syndrome in neoplastic disease
	P940	Transient neonatal myasthenia gravis
12. FNAIT: Fetal and Neonatal alloimmune thrombocytopenia	O3682	Fetal anemia and thrombocytopenia
	P610	Transient neonatal thrombocytopenia
13. Von Willebrand's disease	D680	Von Willebrand's disease
	M33	Dermatopolymyositis
14. Inflammatory myopathies (dermatomyositis ,polymyositis inclusion body myositis, immune-mediated necrotizing myopathy)	M360	Dermato(poly)myositis in neoplastic disease
	G724	Inflammatory and immune myopathies, (inclusion body myositis and other inflammatory and immune myopathies)
15. Stiff-person syndrome	G2582	Stiff-person syndrome
16. Red cell aplasia (Erythroblastopenia)	D60 (+B976)	Acquired pure red cell aplasia [erythroblastopenia] (+Parvovirus as the cause of diseases classified elsewhere)
17. Pemphigus (vulgaris-foliculae)-immunobullous disease	L100	Pemphigus vulgaris
	L102	Pemphigus foliaceus
18. Posttransfusion purpura	D6951	Posttransfusion purpura
19. Antibody-mediated types of encephalitis	G0481	Other encephalitis and encephalomyelitis

* Countries considered included "Australia, Canada, England and France". These were selected given their recent activities in reviewing this field.