

The Use of Intravenous Immunoglobulins in Belgium

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Key Words

Immunoglobulins, intravenous • Off-label use • Reimbursement • Belgium

Abstract

Background: In light of the limited supply of intravenous immunoglobulins, it is important to strive for their appropriate use. Off-label use needs to be discouraged because of the limited supply of intravenous immunoglobulins, their unproven effectiveness in many conditions, their high costs, and the risk of adverse effects. This study aims to document the use of intravenous immunoglobulins in registered and off-label conditions in Belgian hospitals. **Methods:** Data were derived from the IMS Health hospital disease database. For each condition, this database generated figures about the number of patients and the reimbursement value in 2007. Data were provided at the level of individual products. **Results:** In 2007, intravenous immunoglobulins were administered to 9,629 patients, amounting to a reimbursement value of EUR 33.5 million (or 17% of Belgian hospital drug expenditure). Around 50–60% of intravenous immunoglobulin use was associated with registered conditions and around 40–50% with off-label use, depending on how use was measured. Off-label use occurred in unspecified conditions, surgery, orthopedics and oncology. There was limited use in myasthenia gravis. The market was dominated by Multigam and Sandoglobuline, each of which made up 45–50% of intravenous immunoglobulin use. **Conclusions:** In addition to their use in registered conditions, intravenous immunoglobulins are used off-label in other conditions in Belgium. A

number of options are proposed to discourage off-label use in light of the limited supply of intravenous immunoglobulins, their unproven effectiveness in many conditions, their high cost, and the risk of adverse effects.

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Introduction

Intravenous immunoglobulins (IVIGs) have been approved for use in a limited number of conditions [1]. Additionally, IVIGs are used off-label in nearly 100 conditions [2]. The off-label use of IVIGs may originate from the fact that their mechanism of action is not fully understood, that they are used in conditions that are suspected to have an autoimmune etiology, or that they are used as a last resort when other treatment approaches have failed [3]. The aim of this study is to document the use of IVIGs in Belgium with a view to quantifying their use in registered conditions and off-label use in hospitals.

Material and Methods

Data on IVIG use in Belgian hospitals were derived from the IMS Health hospital disease database. For each condition, this database generated figures about the number of patients and the value reimbursed by the RIZIV/INAMI, the Belgian third-party payer, for the year 2007. Data were provided at the level of individual products, i.e. Gammagard S/D, Multigam, Octagam and Sandoglobuline.

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Fig. 1. IVIG off-label use in Belgium in 2007. **a** Patients using IVIG. **b** Reimbursement value.

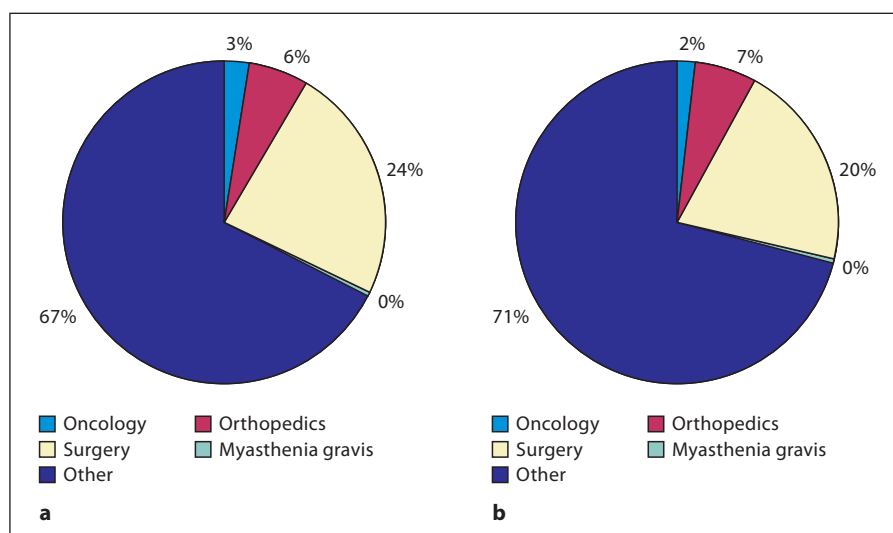


Table 1. IVIG use in Belgium in 2007

	Number of patients		Reimbursement value	
	absolute	relative	absolute, EUR	relative
Primary immunodeficiency	2,293	24%	7,764,023	23%
AIDS	13	0%	58,736	0%
Bone marrow transplantation	109	1%	228,571	1%
Chronic neurology	750	8%	5,361,793	16%
Secondary immunodeficiency	1,385	14%	3,769,579	11%
Kawasaki disease	109	1%	134,433	0%
Idiopathic thrombocytopenic purpura	533	6%	2,375,324	7%
Off-label conditions	4,437	46%	13,802,870	41%
Total	9,629	100%	33,495,328	100%

The analysis considered IVIG use in registered conditions and off-label use. Registered conditions were grouped as follows: primary immunodeficiency, AIDS, bone marrow transplantation, chronic neurology (e.g. chronic inflammatory demyelinating polyneuritis, peripheral neuropathies, and Guillain-Barré syndrome), secondary immunodeficiency (e.g. chronic lymphoid leukemia, multiple myeloma, myeloid leukemias, and acute lymphoid leukemia), Kawasaki disease, and idiopathic thrombocytopenic purpura. Use in other conditions does not correspond with the Summary of Product Characteristics and was considered to be off-label use. Off-label conditions were grouped in terms of oncology, orthopedics, surgery, and other unspecified conditions.

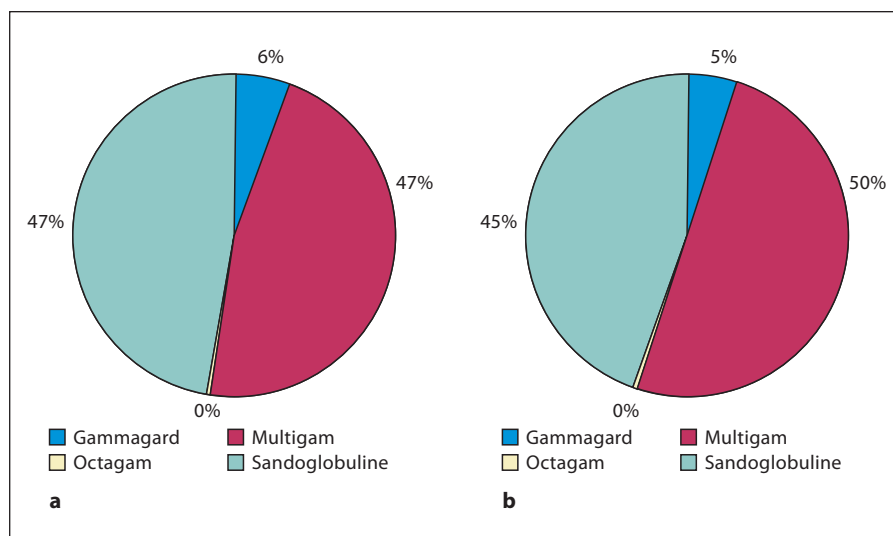
In order to collect these data, IMS Health carried out an analysis of a nationally representative sample of 47 hospitals in 2007. For reasons of confidentiality, IMS Health does not name the hospitals included in the sample, although some of their characteristics are known: the hospital sample accounted for 1.7 million hos-

pitalizations, 1.1 million admitted patients, 7.9 million diagnoses and 16.2 million product codings. The 47 hospitals represented 34% of all hospital beds in Belgium. The sample of hospitals included acute hospitals of different sizes as well as university hospitals in the Dutch-speaking and French-speaking parts of Belgium.

Results

In 2007, the RIZIV/INAMI reimbursement value of IVIG use in Belgian hospitals amounted to EUR 33.5 million (see table 1). IVIG therapy was administered to 9,629 patients. The breakdown of IVIG use according to condition showed similar results irrespective of whether IVIG

Fig. 2. IVIG use in Belgium in 2007 by product. **a** Patients using IVIG. **b** Reimbursement value.



use was measured in terms of the number of patients or the reimbursement value. For instance, reimbursement of IVIG use was related to – in descending order of value – off-label conditions (41%), primary immunodeficiency (23%), chronic neurology (16%), secondary immunodeficiency (11%), idiopathic thrombocytopenic purpura (7%), and bone marrow transplantation (1%). IVIG had not been administered in the treatment of AIDS or Kawasaki disease.

Patient numbers and the RIZIV/INAMI reimbursement value associated with off-label use of IVIG in Belgium in 2007 are shown in figure 1. The majority of off-label use of IVIG occurred in unspecified conditions. Additionally, off-label use was situated in the domains of surgery (e.g. digestive surgery, vascular surgery, surgery aftercare, and obstetrical surgery), orthopedics (e.g. dorsopathies and other fractures), and oncology (e.g. lung cancer, breast cancer, colorectal cancer, prostate cancer, and other solid cancers). There was limited use of IVIGs in myasthenia gravis, an autoimmune neuromuscular disease.

Figure 2 presents data on IVIG use (measured in terms of patient numbers and the RIZIV/INAMI reimbursement value) in Belgian hospitals in 2007 broken down by product. The results indicate that the market is dominated by Multigam and Sandoglobuline, each of which makes up 45–50% of IVIG use. Around 5–6% of IVIG use originates from Gammagard S/D. Octagam is used in the treatment of primary immunodeficiency only, accounting for 30 patients and a reimbursement value of EUR 57,000.

Discussion

This analysis has documented the use of IVIGs in registered conditions and its off-label use in Belgian hospitals in 2007. Primary immunodeficiency is the major labeled condition for IVIG therapy, but off-label conditions represent an important application of the use of IVIG in clinical practice. Around 50–60% of IVIG use was associated with registered conditions and around 40–50% was associated with off-label use, depending on how IVIG use was measured. Other studies in the literature estimate off-label use to make up 50–70% of IVIG consumption [2, 4, 5]. As chronic inflammatory demyelinating polyneuropathy was recently approved as a new indication for IVIG therapy and included among the registered indications in our analysis, the estimates of off-label use of previous studies were higher than our estimates. Also, in contrast to previous studies that quantified IVIG use in a few hundred patients, this study extrapolated data from a sample consisting of 47 hospitals and around 10,000 patients, to the Belgian level.

IVIG use in registered conditions was principally related to primary and secondary immunodeficiency and to chronic neurology. Evidence of the efficacy of IVIG therapy in these conditions has been published, even though the quality of this evidence is variable [6]. IVIG off-label use occurred in the domains of surgery, orthopedics, oncology and myasthenia gravis. Literature reviews found some evidence supporting the use of IVIG as second-line therapy for myasthenic crises, but the use in surgery, orthopedics and oncology is not recommended until evi-

dence of the efficacy of IVIG therapy in these conditions has been gathered by means of controlled trials [3, 4].

When focusing on individual products, the findings showed that Multigam and Sandoglobuline account for the majority of IVIG consumption. This may change when the next generation of 10% liquid IVIGs enters the market in the coming years [7]. Our analysis was able to distinguish between individual products, but the IMS Health hospital disease database did not contain information about the reasons for prescribing specific products. Prescribing patterns may differ between Belgian hospitals because of the existence of hospital-specific drug formularies that tend to list one commercial preparation available for prescription. In general, few differences exist between individual products in terms of effectiveness and cost-effectiveness [8], except for their use in patients with specific characteristics (e.g. a patient with an adverse reaction to one product or a patient with a specific metabolic deficiency). Our analysis also computed the RIZIV/INAMI reimbursement value of IVIG consumption in Belgian hospitals. IVIG therapy accounted for EUR 33.5 million or around 17% of the reimbursement value of all drugs administered to hospitalized patients in Belgium of EUR 202 million in 2007.

This study suffers from a number of limitations. First, a patient may receive hospital treatment for multiple indications, such as, for example, primary immunodeficiency and a surgical condition. If such a patient receives IVIG therapy, the IMS Health hospital disease database may classify IVIG therapy under the registered indication of primary immunodeficiency or the off-label indication of the surgical condition. This implies that the level of off-label use of IVIG therapy is likely to be overestimated by IMS data. Second, off-label conditions were grouped in

terms of oncology, orthopedics, surgery and other unspecified conditions in the absence of information on more detailed diagnoses. Third, if tertiary care centers would disproportionally prescribe more IVIG, a nonparametric analysis of the analyzed sample would be called for. However, IMS Health does not provide information about the specific statistical tests employed to compare the hospital sample to the actual range of hospital types in the population to which the data were extrapolated. Despite these limitations, the analysis drew on IMS data because it is the only data source available to researchers to investigate the use of IVIG therapy at a national level.

Off-label use of IVIG needs to be discouraged in light of the limited supply of IVIG and of donor plasma, the unproven effectiveness of IVIG in many conditions, the high costs of IVIG therapy, and the risk of adverse effects. A number of measures can be taken to promote the appropriate use of IVIG. There is a need to establish registries with a view to gaining insight into the conditions in which IVIG is used and to assessing its safety and effectiveness in those conditions. The use of evidence-based guidelines, feedback to stakeholders, and preprinted ordering forms has been associated with a decrease in inappropriate IVIG use and with cost savings in a number of Canadian provinces [9]. Physicians need to be informed about IVIG indications and off-label use. National consensus statements on the appropriate use of IVIG and the establishment of standards for use may be called for.

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