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Direct Medical Costs of Liquid Intravenous Immunoglobulins in Children, Adolescents, and Adults in Spain

Josep Darbà, PhD, Gabriela Restovic, MSc, Lisette Kaskens, MSc,
and Tuy de Agustín, MD

The aim of this study was to determine health care resource utilization and direct medical costs in Spanish patients treated with intravenous immunoglobulins (IVIGs) in 2009. Cost-of-illness analyses were performed to estimate direct medical costs of patients treated with IVIGs. Prevalence data were obtained from the Spanish Primary Immunodeficiency registry. A semi-structured questionnaire was used to collect data on health care resource utilization and patient distribution. Drug, administration, and premedication costs were considered from the payer's perspective. Separate analyses were conducted for children and adolescents versus adults. The numbers of children and adolescents with replacement therapy were 724, with immunomodulation 243, and with allogeneic bone marrow transplantation 30. The numbers of adult patients were, respectively, 3450, 1134, and 172. Mean

annual costs for children and adolescents were 6293 € with Privigen, 6292 € with Kiovig, 6939 € with Flebogamma, and 6559 € with Octagamocta. For adults, estimations were 17 106 € with Privigen, 17 103 € with Kiovig, 18 077 € with Flebogamma, and 17 423 € with Octagamocta. Direct medical costs for IVIGs were approximately 91.8 million €. Drug costs represented 94% of total costs. The choice for a certain IVIG treatment depends on individual patient characteristics and cost considerations.

Keywords: Intravenous immunoglobulin; costs; cost of illness; replacement therapy; immunomodulation; allogeneic bone marrow transplantation

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Intravenous immunoglobulin (IVIG) is a fractionated blood product used in the treatment of a variety of diseases. IVIG preparations are produced from pooled human plasma from several thousand screened blood donors. These preparations contain primarily pooled immunoglobulin G (IgG) but also traces of other immunoglobulins.^{1,2} Intravenous administration allows large doses of immunoglobulin to be given and therefore facilitates a rapid onset of action. IVIGs have shown to be effective and reliable.³⁻⁶ The mechanisms of action of therapeutic immunoglobulin are complex, but in recent years important advances in their understanding have been made including both the immunoglobulin dose and the pathogenesis of the disease under consideration.

IVIGs have been approved by the European Agency for the Evaluation of Medicinal Products (EMA) for certain conditions in which their efficacy and safety have been proven in well-controlled clinical trials.¹ These indications are known as labeled. However, there are an ever-increasing number of indications for which the use of IVIGs is proposed.^{7,8}

In Spain, only some indications for the use of IVIGs have been authorized by the Spanish Medicines Agency on the basis of contributed evidence.⁹ The authorized indications include replacement therapy and the subindications primary immunodeficiency (PID), secondary immunodeficiency (SID), and congenital AIDS in children (treatment of recurrent infections). The indications also include immunomodulation and the subindications idiopathic thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), and Kawasaki disease. A third authorized indication is allogeneic bone marrow transplantation. Within Spain, IVIGs are also used for a number of conditions not included in regulatory approvals and as a consequence are used off-label with or without clinical scientific evidence supporting their use.^{1,9}

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The dose and frequency of infusions with IVIGs depend on the disease to be treated. In replacement therapy, it may be necessary to adjust the dose according to the patient's response. Doses also differ depending on weight and age of a patient.

IVIG is used mainly at high dose (2 g/kg) for the indications in neurology, hematology, rheumatology, dermatology, and others, whereas in immunology replacement doses (0.4 g/kg) are given.²

In the setting of genetic or acquired immune deficiencies, the mechanism of action of IVIG is straightforward. In replacement therapy for PID, IVIG treatment is the mainstay of therapy for infections and patients requiring lifelong immunoglobulin therapy.¹⁰ IVIG therapy replaces functional or deficient IgG, which reduces the incidence of infections and prevents organ damage caused by recurrent infection.¹¹ Therefore, IVIGs provide the body with an important defense mechanism against infectious agents. When IVIG treatment is used as an immunomodulating agent in immune-mediated diseases, the mechanism of action is less clearly defined, although substantial progress has been made in the understanding of this mechanism.¹

The use of IVIGs has increased significantly in recent years^{12,13} and is still increasing.^{14,15} IVIGs have shown to be costly.¹⁶ The price per unit of IVIG has increased significantly because of the increased complexity of the manufacturing processes as well as safety enhancements and stringent regulatory requirements. The capacity to fractionate IVIG from plasma is finite, and regulatory stringency has resulted in major recalls of the product by many of the important worldwide manufacturers. These factors, together with the increase in use, have led to significant worldwide shortages of IVIG in the last few years.^{2,17-19} The demand for IVIG is constantly increasing, with a worldwide increase in use of 15% to 18% per year reported in recent years.²⁰ An explanation for this increase could be that IVIG preparations are being used in a wider range of diseases than only those authorized or supported by evidence.¹

The increase in consumption of IVIGs and its high cost promote their rational use.²¹ When selecting an IVIG therapy, it is important to consider several factors apart from the drug costs that add to the total treatment costs of IVIGs. The effect of these factors becomes even greater over time in cases where long-term therapy is needed but also in other indications where treatment is generally more frequent, doses are higher, and infusion times are longer. Factors as a reduced infusion time due to the differences in IVIG preparations; a ready-to-use liquid solution

versus a to solve powder affects the time spent by health personnel and will therefore lead to substantial cost savings. Also, an effective and better tolerated IVIG treatment allows a faster infusion speed, which will reduce infusion, nursing, and bed-occupancy time, reducing overall treatment costs.¹¹

To better understand the economic impact of IVIG treatments, we can examine the economic burden of these treatments and their associated costs. A cost-of-illness study measures the economic burden of a disease or diseases and estimates the maximum amount that could potentially be saved or gained if a disease were eradicated. Such a study highlights the magnitude of the impact of an illness on society.²² Knowledge of the costs of an illness can help policy makers decide which diseases need to be addressed first by health care and prevention policy. Additionally, these studies can indicate for which diseases cures would be valuable in reducing the burden of disease.

The aim of this study is to determine the health care resource utilization and direct medical costs associated with different liquid IVIG treatment options in Spain in 2009 from the perspective of the Spanish National Health Care System. In Spain, IVIG treatments are hospital-only products that are entirely funded by the hospital. Resources considered were the costs of liquid IVIG treatments, administration costs, hospitalization, and premedication. The target populations in our study are restricted to the authorized indications for IVIGs in Spain.

METHODS

A cost-of-illness analysis was performed to estimate annual direct medical costs of patients treated with IVIGs in Spanish hospitals. The analysis included the identification, measurement, and evaluation of all resources related to an illness treated with IVIGs.

We estimated the use of health care resources in children, adolescents, and adults receiving IVIG treatment for authorized indications in Spain in order to determine the cost-of-illness in actual medical practice.

The analysis adopted a prevalence approach within an annual time frame, whereby all costs within the most recent year for which data were available were measured, regardless of the disease onset. All health care costs were adjusted to 2009 prices.

Data Sources

Spanish epidemiologic data were obtained from a literature search. The dosage and frequency of

administration of IVIGs for the included indications were estimated from clinical prospects.

The health care resources used in each treatment were estimated by a panel of 5 clinical experts from different Spanish autonomous regions in Spain, including a hospital pharmacist, neurologists, and immunologists. Data were gathered using a semi-structured questionnaire.

Unit costs for visits and hospitalizations were obtained from Spanish literature and were adapted to euros for December 2009. Drug costs for IVIGs and premedication were obtained from different local medication databases.

Perspective

The present analysis considered the payer perspective of the Spanish National Health Care System. Costs considered in this study included direct medical costs.

Population

The target population in this study was determined by the approved indications for the use of IVIGs in Spain. IVIG therapy is given as replacement therapy, for immunomodulation, and for allogeneic bone marrow transplantation, with their respective subpopulations. For replacement therapy, subindications were PID, SID, and AIDS in children. The subindications for immunomodulation were ITP, GBS, and Kawasaki disease. For allogeneic bone marrow transplant, no subindications were distinguished. See Table I for overview of the main indications and subindications included in this study.

The treatment populations considered in this study were children, adolescents, and adults. A differentiation was made between children and adolescents (<18 years old) and adults (>18 years old).

The total treatment population with replacement therapy, immunomodulation, and allogeneic bone marrow transplantation and their respective subpopulations treated with IVIGs were estimated for 2009. The Spanish Registry of Primary Immunodeficiencies reports the number of patients with PID for each year.²³ Distributions of patients with IVIG treatment for all indications in this study were obtained from the expert panel. The distributions for the main indications were as following: 73% for replacement therapy, 24% for immunomodulation and 3% for allogeneic bone marrow transplant. See the overview of patient distributions for main indications and subindications in Table II.

Table I Overview of Main Indications, Subindications, Administration Doses, and Frequency of Intravenous Immunoglobulins in Spain

Indication	Dose, g/kg	Frequency
Replacement therapy		
Primary immunodeficiency	Initial, 0.4-0.8; following, 0.2-0.8	Every 2-4 weeks to obtain IgG preinfusion of at least 4-6 g/L
Secondary immunodeficiency	0.2-0.4	Every weeks to obtain IgG preinfusion of at least 4-6 g/L
Children with AIDS	0.2-0.4	Every 3-4 weeks
Immunomodulation		
Idiopathic thrombocytopenic purpura	0.8-1 or	The first day, with possibility to repeat after 3 days
	0.4 per day	For 2-5 days
Guillain-Barré syndrome	0.4 per day	For 3-7 days
Kawasaki disease	1.6-2 or	In various doses for 2-5 days in association with ASA
	2	In 1 dose in association with ASA
Allogeneic bone marrow transplantation		
Treatment of infections and prophylaxis of graft vs host disease	0.5	Beginning day 7 before transplant, every week for 3 months after transplant
Persistent lack of antibody production	0.5	Every month until the level of antibodies is normal

ASA, Acetylsalicylic Acid; IgG, immunoglobulin G.

The target population for IVIG treatment was estimated based on data on the total number of PID cases in Spain, patient distribution data for each indication and subindication, data on the national population, and the ratio between the population younger and older than 18 years from the National Statistic Database (INE).²⁴

Treatment Options

Immunoglobulin is obtained from the fractionation of plasma of healthy donors. All manufacturers use

Table II Distribution Target Population for Intravenous Immunoglobulin Treatment According to Indications

Main Indication	Distribution, %	Subindication	Distribution, %
Replacement therapy	73	Primary immunodeficiency	55
		Secondary immunodeficiency	18
		Children with AIDS	0
Immunomodulation	24	Idiopathic thrombocytopenic purpura	14
		Guillain-Barré syndrome	2
		Kawasaki disease	7
Allogenic bone marrow transplantation	3		3
Total	100		100

Table III Overview of Drug Treatments Compared and Their Product Characteristics

Drug	Concentration, %	Maximum Perfusion Velocity, mL/kg/h
Privigen	10	7.2
Kiovig	10	8.0
Flebogamma	5	2.4
Octagamocta	5	<4.2

a similar technique that consists of plasma fractionation in cold ethanol. The different IV products are distinguished by the method of purification used; a general requirement is that monomeric IgG molecules constitute at least 90% of the total IVIG treatment. The concentration of immunoglobulin A is the minimum possible, and IgG subclasses maintain a profile similar to human plasma and do not contain preservatives such as plasmin and kinin.

The IVIGs considered in the study are the following liquid ready-to-use solutions: Privigen (10%), Kiovig (10%), Flebogamma (5%), and Octagamocta (5%). Each of these products has a maximum perfusion velocity, and it is assumed that the initial perfusion velocity of all of these products is 0.3 mL/kg/h. The perfusion velocity is doubled every 30 minutes until the maximum velocity is reached. See an overview of the perfusion velocities of all products in Table III.

Use of Resources and Costs

Only direct health care resources associated with IVIG treatment were considered; they included drug treatment and the time to administer drug and premedication. Total treatment costs for each of the

4 treatments were estimated using data from local published literature and information gathered by the consultation of clinical experts.

Resource utilization was evaluated for each disease and IVIG treatment. Drug administration time was defined by the prospectus of each IVIG treatment, and premedication administration time was estimated based on the responses of clinical experts.

For all 4 IVIG treatments, the same indications were considered. Drug therapy doses were obtained from the prospectus for each indication. In medical practice, IVIG administration doses depend on a patient's weight and age, so separate analyses were conducted for children and adolescents versus adults.

Drug prices for IVIGs were obtained from Vademecum,²⁵ and premedication costs were obtained from the Spanish Medication database,²⁶ for the year 2009. Prices were used to calculate the average annual drug treatment costs for each drug for patients younger than 18 years and patients older than 18 years. The average drug prices of all presentations available were used to estimate the average IVIG treatment costs per year and are shown in price per gram of IVIG in Table IV.

The main unit costs in this study related to the administration of IVIGs and premedication are presented in Table V. Administration costs were estimated based on the concentration and rate of administration of each IVIG. Total administration time included the time of drug administration as well as the recovery time after administration. Recovery time after administration was estimated from responses by clinical experts.

Depending on each IVIG treatment as well as the disease to be treated, the administration of IVIG takes place during hospitalization in a day hospital for a few hours several days per year or during

Table IV Pharmacological Treatment Costs 2009

Drug Treatment	Volume Per Vial or Bottle, mL	Grams Per Vial or Bottle	Manufacturer Selling Price, €	Manufacturer Selling Price/Gram, €
Privigen	100	10	409.00	40.90
	25	2.5	102.25	40.90
	200	20	818.00	40.90
	50	5	204.50	40.90
Kiovig	10	1	40.90	40.90
	100	10	409.00	40.90
	25	2.5	102.25	40.90
	200	20	818.00	40.90
Flebogamma IV (5%)	50	5	204.50	40.90
	10	0.5	20.96	41.92
	50	2.5	104.76	41.90
	100	5	210	42.00
Octagamocta	200	10	420	42.00
	100	5	204.50	40.90
	200	10	409.00	40.90
	50	2.5	102.25	40.90

Source: Vademecum. <http://www.vademecum.es>. Accessed September 8, 2010.

Table V Unit Costs 2009

Resources Used	Average Cost in Spain, €
Visit to nurse ^a	14
Nurse (1 h) ^b	12
Nurse (minutes) ^b	0.2
Hospitalization (1 day) ^a	267
Premedication	Manufacturer Selling Price, €/mg
Prednisone (10 mg, 30 tablets) ^c	0.00543
Ibuprofen (600 mg, 40 tablets) ^c	0.00005
Dalsy (oral suspension 200 mL, 100 mg/5 mL) ^c	0.00050
Paracetamol (1 g, 20 tablets) ^c	0.00006
Apiretal (oral suspension 90 mL, 100 mg/mL) ^c	0.00029
Dexchlorpheniramine (Polaramine 6 mg/20 tablets) ^c	0.02617

a. From DOGC no. 4540-30/12/2005 http://www.gencat.cat/diari_c/4540/05347104.htm. Accessed August 9, 2010.

b. From DOGC no. 4932 24/07/2007 http://www.gencat.cat/diari_c/4932/07192013.htm. Accessed August 9, 2010.

c. From CGCOF: medicine database. Consejo General de Colegios Oficiales de Farmacéuticos. <http://www.portalafarma.com>. Accessed August 9, 2010.

hospitalization in days per year. Day hospitalization for a few hours during each hospitalization was calculated as the time that a nurse was present during IVIG treatment. For hospitalization for several days, the unit cost was taken for hospitalization.

The different unit costs are shown in Table V. The administration costs are equal to the total time necessary for administration of IVIGs depending on the place of administration, each IVIG treatment, and the indication concerned. A distinction was made in costs for patients younger than 18 years and patients older than 18 years.

The cost of premedication was considered dependent on both the IVIG treatment and indication concerned and the percentage of patients and age of the patient who required such premedication. The percentage of patients requiring premedication for each indication was estimated from the responses by clinical experts and was found to be 12% for the whole treatment population. Doses of premedication varied depending the age of the patient as well as the disease concerned. For each IVIG treatment according to indication and age group, an average cost for premedication was calculated. See Table V for an overview of the type of premedication given to patients and the unit cost.

Analysis Overview

The average treatment cost per treatment strategy and indication per year was estimated for patients younger than 18 years and patients older than 18 years based on health care resource utilization, unit cost, and indication for each IVIG treatment. With the average treatment cost per strategy and the

Table VI Total Target Population

Total Spain	Total Cases	Patients <18 Years Old	Patients >18 Years Old
I. Replacement therapy			
Primary immunodeficiency	3144	557	2588
Secondary immunodeficiency	1048	186	863
Children with AIDS	0	0	0
II. Immunomodulation			
Idiopathic thrombocytopenic purpura	827	146	681
Guillain-Barré syndrome	138	24	113
Kawasaki disease	413	73	340
III. Allogeneic bone marrow transplant	172	30	142
Total target population	5743	1017	4726

prevalence for each indication, the total cost of illness for all treatment strategies and indications was estimated according to their corresponding market share. The market shares for 2009 assumed for all 4 IVIG treatments in this study were 2% Privigen, 9% Kiovig, 85% Flebogamma, and 4% Octagamocta.

RESULTS

Target Population

The total target population for IVIG treatment was based on extrapolated data, which allowed us to estimate the prevalence of patients in each indication as shown in Table VI.

In 2009, the total Spanish target treatment population for IVIGs for all indications explored in this study was estimated to be 5743, of which 1017 were older than 18 years and 4726 were older than 18 years. The highest number of patients for IVIG treatment reported was for replacement therapy, with a total number of 4192 patients; per subindication this resulted in 3144 patients with PID and 1048 patients with SID. Based on consultations with experts, no IVIG treatments were estimated to be given to children with AIDS. Per age group this resulted in 557 patients with PID and 186 with SID for patients younger than 18 years and 2588 patients with PID and 863 with SID for patients older than 18 years.

The number of patients with immunomodulation estimated to be treated with IVIGs was 1378. Per subindication in the patients younger than 18 years, this resulted in 146 patients with ITP, 24 patients with GBS, and 73 patients with Kawasaki disease. In patients older than 18 years, 681 patients had ITP, 113 patients had GBS, and 340 patients had Kawasaki disease.

The number of patients with allogeneic bone marrow transplantation treated with IVIGs was estimated at 172, of whom 30 patients were younger than 18 years and 142 patients were older than 18 years.

Total Annual Treatment Costs for Each IVIG Treatment for Each Indication

Based on epidemiological information, drug and premedication costs for each IVIG treatment, and the health care resources used, the total annual treatment costs were estimated for each IVIG treatment and each indication. A distinction was made for patients younger than 18 years and patients older than 18 years. An overview of the total treatment costs per indication for both age groups per IVIG treatment is shown in Table VII.

Total Cost of Illness of Treatment With IVIGs

Based on the total treatment costs per IVIG treatment and their respective market shares, the economic burden for IVIG treatment for 2009 was estimated (Table VIII).

Total cost for treatment with Privigen was estimated to be 1 744 802 €, with costs of 1 693 667 € for IVIGs, 215 € for premedication, and 50 920 € for their administration time. From the total cost associated with Privigen, 1 279 44 € was the cost for patients younger than 18 years and 1 616 857 € was for patients older than 18 years.

Total cost for treatment with Kiovig was estimated to be 7 850 333 €, with costs of 7 621 501 € for IVIGs, 969 € for premedication, and 227 864 € for their administration time. From the total cost associated with Kiovig, 575 613 € was the cost for patients younger than 18 years and 7 274 720 € was for patients older than 18 years.

Table VII Average Treatment Cost Per Year (€) for Each Intravenous Immunoglobulin Treatment Per Indication and Age Group

Treatment and Patient Age	Cost Category	PID	SID	Children With AIDS	ITP	Disease of Kawasaki	GBS	Allogenic Bone Marrow Transplant	
Privigen <18 y	Pharmacological treatment	8242	3821	4471	1718	1636	2454	6646	
	Administration	580	352	394	96	54	144	385	
	Premedication	0.91	3.63	0.75	3.53	0.42	0.10	0.66	
	Total per year	8823	4177	4865	1817	1691	2598	7032	
	>18 y	Pharmacological treatment	23 297	12 688	0	3722	5317	5590	17 280
		Administration	586	446	0	107	268	162	428
		Premedication	2.38	0.72	0	2.10	0.47	0.90	3.23
		Total per year	23 885	13 135	0	3831	5586	5752	17 712
Kiovig <18 y	Pharmacological treatment	8242	3821	4471	1718	1636	2454	6646	
	Administration	579	349	393	95	53	142	380	
	Premedication	0.91	3.63	0.75	3.53	0.42	0.10	0.66	
	Total per year	8822	4174	4864	1816	1689	2597	7027	
	>18 y	Pharmacological treatment	23 297	12 688	0	3722	5317	5590	17 280
		Administration	584	441	0	105	268	159	427
		Premedication	2.38	0.72	0	2.10	0.47	0.90	3.23
		Total per year	23 883	13 131	0	3829	5586	5749	17 710
Flebogamma <18 y	Pharmacological treatment	8455	3920	4586	1762	1678	2517	6818	
	Administration	1367	460	451	187	537	267	738	
	Premedication	0.95	3.53	0.79	3.60	0.56	0.04	0.69	
	Total per year	9822	4384	5038	1953	2215	2785	7556	
	>18 y	Pharmacological treatment	23 898	13 016	0	3818	5454	5734	17 726
		Administration	1441	586	0	205	537	296	1036
		Premedication	2.50	0.48	0	3.23	0.63	0.33	3.23
		Total per year	25 341	13 602	0	4027	5991	6030	18 765
Octagamocta <18 y	Pharmacological treatment	8242	3821	4471	1718	1636	2454	6646	
	Administration	974	436	423	181	270	258	695	
	Premedication	0.95	3.53	0.79	3.60	0.56	0.04	0.69	
	Total per year	9217	4261	4895	1902	1906	2712	7342	
	>18 y	Pharmacological treatment	23 297	12 688	0	3722	5317	5590	17 280
		Administration	1089	506	0	191	270	274	786
		Premedication	2.50	0.48	0	3.23	0.63	0.33	3.23
		Total per year	24 388	13 195	0	3916	5587	5864	18 070

SID, secondary immunodeficiency; GBS, Guillain-Barré syndrome; ITP, idiopathic thrombocytopenic purpura; PID, primary immunodeficiency.

Table VIII Estimated Total Economic Burden for Intravenous Immunoglobulin (IVIG) Treatments in Spain in 2009

Health Economic Burden	Total Costs for 2009	Total Costs for Patients <18 Years Old	Total Costs for Patients >18 Years Old
Privigen			
Pharmacological treatment	1 693 667	119 397	1 574 270
Administration of IVIGs	50 920	8 512	42 407
Premedication	215	35	181
Kiovig			
Pharmacological treatment	7 621 501	537 288	7 084 213
Administration of IVIGs	227 864	38 170	189 694
Premedication	969	156	813
Flebogamma			
Pharmacological treatment	73 839 323	5 205 401	68 633 922
Administration of IVIGs	4 767 983	789 256	3 978 727
Premedication	9748	1487	8261
Octagamocta			
Pharmacological treatment	3 387 334	238 795	3 148 539
Administration of IVIGs	172 577	27 836	144 740
Premedication	459	70	389
Total economic burden	91 772 558	6 966 402	84 806 156

Total cost for treatment with Flebogamma was estimated to be 78 617 054 €, with costs of 73 839 323 € for IVIGs, 9748 € for premedication, and 4 767 983 € for their administration time. From the total cost associated with Flebogamma, 5 996 143 € was the cost for patients younger than 18 years and 72 620 910 € was for patients older than 18 years.

Total cost for treatment with Octagamocta was estimated to be 3 560 369 €, with costs of 3 387 334 € for IVIGs, 459 € for premedication, and 172 577 € for their administration time. From the total cost associated with Octagamocta, 266 701 € was the cost for patients younger than 18 years and 3 293 668 € was for patients older than 18 years.

The total economic burden for IVIG treatment in 2009 was estimated to be 91 772 558 million €, of which 6 966 402 € was for patients younger than 18 years and 84 806 156 € for patients older than 18 years.

Of the total cost for each IVIG treatment, IVIG costs are the largest part of overall treatment costs. An average 94% of all treatment costs were for drug: for Privigen and Kiovig, drug costs were 97% of total treatment costs, for Flebogamma 94%, and for Octagamocta 95%.

Average Treatment Cost Per Patient Per IVIG Treatment

Based on the total treatment cost for each IVIG treatment, average treatment cost per patient for 2009 was

calculated, independent of the indication. Average annual treatment cost was also calculated per age group.

The total average annual treatment costs including all IVIG treatments per patient were estimated at 15 981 € for the total target population, 6853 € for patients younger than 18 years, and 17 944 € for patients older than 18 years. Average annual treatment costs per patient per year for those treated with Kiovig and Privigen were almost the same, with 15 189 € for Kiovig and 15 192 € for Privigen. Average treatment cost per patient for those treated with Flebogamma was the highest, with 16 122 € per year. Similar results were reported for patients younger than 18 years and older than 18 years. See Table IX for an overview of average annual treatment costs per patient per IVIG treatment for both age groups.

DISCUSSION

Cost-of-illness studies give insight in the economic burden of a disease. Knowledge of the economic burden can help policy makers decide which diseases to address and how to address these to reduce their burden. The objective of this study was to determine the health care resource utilization and direct medical costs for patients treated with liquid, ready-to-use IVIGs for the authorized indications in Spain for 2009.

The results of this study showed that the total economic burden of IVIG treatments in 2009 including

Table IX Average Annual Treatment Costs (€) for Intravenous Immunoglobulin (IVIG) Treatment for 2009

Treatment	Total Cost	Patients <18 Years Old	Patients >18 Years Old
Privigen	15 192	6293	17 106
Kiovig	15 189	6292	17 103
Flebogamma	16 106	6939	18 077
Octagamocta	15 500	6559	17 423
Average all IVIG treatments	15 981	6853	17 944

Privigen, Kiovig, Flebogamma, and Octagamocta was an estimated 91.8 million € for the Spanish National Health Care System in the authorized indications. Total cost for patients with IVIG treatment younger than 18 years was 6.9 million € and for patients older than 18 years was 84.8 million €.

The economic burden in the current scenario of these 4 IVIG treatments was estimated using market shares of Privigen, Kiovig, Flebogamma, and Octagamocta. Comparing the average annual treatment cost per patient for each IVIG treatment separately showed that in the current scenario, total costs for treatment with Kiovig and Privigen were similar, respectively, 15 189€ and 15 192€ per patient per year. The highest cost was reported for Flebogamma: 16 106€ per year.

At present Flebogamma has the highest market share, with 85%. If the market share of Privigen increases from 2% annually to 12% in the coming 5 years, with an increase of 2% per year at the expense of the market share of Flebogamma solely, this would result in direct savings for the Spanish health care system. Total cost savings are estimated to be 1.7 million €, taking in account a discount rate of 3% and an increase of the target population, including all direct health care costs associated with IVIG treatment.

No other published cost analyses quantifying direct health care costs, including all authorized indications together or independently, as in this study, have been identified. Determining the economic burden for immunoglobulins is difficult for several reasons. Limited epidemiologic data are available on the number of cases of replacement therapy, immunomodulation, and allogeneic bone marrow transplantation in Spain. Few studies are available with local, hospital-level data on the number of patients treated with IVIGs.^{9,27} To estimate the target population, an expert panel was consulted and data were extracted from the Spanish PID registry.

In this study, only authorized indications were included to estimate the economic burden of IVIG treatments. From expert consultations, we learned that IVIGs are also prescribed in an increasing

number of off-label indications with or without the support of scientific evidence. Therefore, the real economic burden for IVIG treatments in Spain could even be higher. In 2006, Perayre et al¹ reported that of the total 1332 IVIG treatments administered in a 930-bed hospital in Spain over the previous 5 years, 85.8% of the IVIG prescriptions were for labeled indications whereas 10.2% were for scientifically supported off-label indications and 4% were for indications without evidence. No significant increase in IVIG use was detected in their hospital, and no significant increase was observed in the number of off-label indications for which IVIG was prescribed. Ruiz-Antorán et al,⁹ in an observational, prospective, multicenter drug utilization study published in 2010, reported 1287 prescriptions of any IVIG administered among 554 patients during a 3-month period. Of these prescriptions, 74% were for authorized indications of IVIGs, 11% were off-label with scientific supporting evidence, and 15% were for nonauthorized and nonaccepted indications. These results support the evidence that off-label prescriptions add substantially to the economic burden of IVIG treatments but that the majority of prescriptions are for authorized indications.

In this study we limited the costs to direct health care costs as drug costs, administration, and premedication. Simoons²¹ suggested that in identifying the economic burden of PID, not only health care costs associated with PID and its treatment but also potential costs of suboptimal or ineffective treatment of PID should be included. Another suggestion is to measure costs preceding PID diagnosis and costs in the period following diagnosis to estimate costs associated with the absence or delay of IVIG therapy. Further research is necessary to estimate the effect of these suggestions on the economic burden of IVIG treatments.

Cost-of-illness studies can demonstrate which diseases may require increased allocation of prevention or treatment resources, although these studies are limited in determining how resources should be allocated, because they do not measure benefits. This study provides the first estimate of the economic burden of

IVIGs in authorized indications in Spain and therefore can be used as an initial analytic tool for making decisions about resource allocation for IVIG treatments.

CONCLUSIONS

Direct medical costs for IVIGs were estimated to be 91.8 million € in total: 6.9 € million for children and adolescents and 84.8 € million for adult patients. Drug costs represented 94% of the total direct medical costs. In the context of limited health care resources, the choice for a certain IVIG treatment depends on individual patient characteristics and cost considerations.

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