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ORIGINAL RESEARCH ARTICLE

Cost minimization analysis of subcutaneous and intravenous immunoglobulin treatment in Italy

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ABSTRACT

Introduction: Human immunoglobulins are the standard of care for patients with immunodeficiencies and represent a first-line treatment for chronic inflammatory demyelinating polyneuropathy (CIDP). This study aimed to evaluate costs associated with facilitated subcutaneous (fSCIG), conventional subcutaneous (cSCIG), and intravenous (IVIG) administration of immunoglobulin in patients with primary or secondary immunodeficiency (PID and SID, respectively) and in patients with CIDP in Italy.

Methods: A cost-minimization analysis from a societal perspective was developed, considering a one-year follow-up. Direct costs included acquisition and administration costs, while indirect costs were evaluated considering productivity loss due to in-hospital IVIG using a Human Capital Approach. The posology considered for immunodeficiency disorders and CIDP was obtained from observational studies and clinical trials, respectively. Subcutaneous and intravenous administration costs were obtained from published literature. Scenario analyses were conducted to test the key assumptions of the model.

Results: This study indicates a potential reduction of annual societal expenditure in Italy of approximately €2,145 and €1,605 with fSCIG treatment in PID patients compared to cSCIG and IVIG, respectively. In SID patients, fSCIG would result in a reduction of societal expenditure of approximately €2,145 and €2,071 compared to cSCIG and IVIG. For CIDP patients, fSCIG treatment would result in a reduction of societal expenditure of €8,060 and €15,873 compared to cSCIG and IVIG, respectively.

Conclusion: The use of fSCIG for patients with PIDs, SIDs or CIDP could lead to a reduction in the direct and indirect costs associated with the treatment of patients.

Keywords: Chronic inflammatory demyelinating polyneuropathy, Cost-minimization analysis, Facilitated subcutaneous immunoglobulin, Immunodeficiency

Introduction

Immunoglobulin replacement therapy is the standard of care for patients with primary immunodeficiencies (*Primary Immunodeficiency Disorder* - PID) with reduced production of antibodies (1) and is recommended by guidelines for the treatment of secondary immunodeficiencies (*Secondary Immunodeficiency Disorder* - SID) of patients who have severe or recurrent infections despite prophylactic oral antibiotic *therapy* (2). PIDs represent a heterogeneous group of rare diseases, characterized by developmental and/or function defects of the immune system (3). Although the clinical manifestations of PID are highly variable, many disorders involve an increased susceptibility to infection. Secondary, or acquired, immunodeficiencies represent a transient or persistent impairment of immune system functions, determined by iatrogenic and/or pathological causes (4). Immune defects from acquired immunodeficiency involve, as in primary immunodeficiencies, an increased risk of serious infections, autoimmune diseases or neoplasms (4).

Immunoglobulin therapy also represents a first-line treatment for chronic inflammatory demyelinating polyneuropathy (CIDP), a rare treatable immune-mediated disorder of the peripheral nervous system usually causing muscle weakness and sensory deficits in all extremities. The latest guidelines from the European Academy of Neurology and the Peripheral Nerve Society recommend corticosteroids or intravenous immunoglobulin (IVIG) as first-line or maintenance therapies for patients with CIDP presenting with disabling symptoms (5). Subcutaneous immunoglobulin (SCIG) is additionally recommended as an alternative maintenance

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therapy for patients with active CIDP who have responded to IVIG (5).

Specifically, in the context of SCIG, there are both conventional subcutaneous immunoglobulin (cSCIG) and facilitated subcutaneous immunoglobulin (fSCIG): the former requires frequent infusions, usually weekly, and due to limitations of the volume administered subcoutanuesly often requires multiple infusion sites (1,6); the later one, fSCIG, consists of two vials: one containing human normal immunoglobulin (immunoglobulin 10% or IG 10%) and the other containing recombinant human hyaluronidase (rHuPH20) (7). rHuPH20 increases the permeability of subcutaneous tissue, allowing for the infusion of larger volumes of immunoglobulins than cSCIG, resulting in longer treatment intervals (up to every 4 weeks). The subcutaneous administration route of cSCIG and fSCIG allows for self-infusion at home, in particular with less frequent infusions associated with fSCIG.

The currently available literature suggests that, in the face of comparable efficacy between SCIG and IVIG, treatment decisions may be more influenced by economic considerations and patient preferences (8-11). In particular, with reference to the fSCIG and cSCIG, administration in a home setting could lead to an improvement in the patient's quality of life, especially in a context where treatment durations are long-term (12).

The aim of the present analysis was to evaluate the differences in economic terms of the different modes of administration of human normal immunoglobulin as maintenance therapy in patients with PID, SID or CIDP relative to the national context.

Methods

The analysis was conducted through the development of a cost minimization model to estimate the direct and indirect costs associated with patients with PID, SID and CIDP being treated with human normal immunoglobulin with intravenous, conventional subcutaneous or facilitated subcutaneous administration. The cost of acquiring immunoglobulins and the cost of subcutaneous and intravenous administration were considered among the direct costs. For the following economic analysis, the most widely used IVIG and cSCIG immunoglobulins in Italy (from market research, Hizentra® and Privigen®, respectively) were considered. With reference to fSCIG, treatment with HyQvia® was considered, as to date this is the only subcutaneous normal human immunoglobulin on the marked allowing monthly treatment due to facilitation with hyaluronidase.

Indirect costs were estimated using the human capital approach, thus valuing the loss of productivity associated with the patient who goes to the hospital to carry out the administration of intravenous immunoglobulins and the loss of productivity associated with the caregiver who accompanies the patient to the hospital for the infusion of immunoglobulins.

The time horizon considered in the analysis was one year.

In order to assess the economic impact of the key assumptions of the model on the results of the analysis, a scenario analysis was conducted.

Direct costs

The annual acquisition cost referred to each immunoglobulin was calculated considering the average monthly dosage, the frequency of administration, an average patient weight of 70 kg and 40 kg for adult and pediatric patients, respectively and the ex-factory price reported in the respective Official Journal (OJ) (13-15). The price referred to each immunoglobulin and reported in the respective OJ is the same for all types of immunoglobulin considered within the analysis (€ 65/g).

With reference to the average monthly dosage of immunoglobulins, for patients with PID and SID, this was identified through research conducted on real-world studies published in the scientific literature with reference to Italy (16,17). The rationale for this choice was based on the assumption that immunoglobulins, both subcutaneous and intravenous, are authorized and have been used for a long time for the treatment of these two conditions at the national level and have accumulated a long experience in clinical practice. The retrospective study conducted by Cinetto et al. in order to evaluate the efficacy and safety of SCIG replacement therapy (conventional and facilitated) in a cohort of patients with PID and SID at the Hematology and Clinical Immunology Unit of the Hospital-University of Padua was used to identify average monthly dosage of cSCIG and the fSCIG referred to patients with PID and SID (16). Of the 102 PID patients enrolled in the study, 44.1% received SCIG 20%, 42.1% SCIG 16% or 16.5%, and 13.7% fSCIG 10%. Of the 131 patients with SID, 57.2% were treated with SCIG 20%, 41.2% with SCIG 16% and 1.5% with fSCIG 10%. At steady state, the average monthly dose of cSCIG and fSCIG was significantly higher in patients with PID (0.31 ± 0,10 g/kg, range 0.16-0.64 g/kg) than in patients with SID (0.25 ± 0.08 g/kg, range 0.07-0.55 g/kg) (Mann–Whitney test, $p < 0.0001$) (Tables 1 and 2). Since the literature has shown that the average monthly dosage of IVIG is not significantly different from the average monthly dosage of cSCIG and fSCIG (1,17), the average monthly dose of IVIG was taken equal to that found in the literature and referred to the cSCIG and fSCIG (Tables 1 and 2). The monthly dose of immunoglobulin administered to patients with PID was calculated by accounting for the distribution of adult and pediatric patients observed in the IPINet registry by Lougaris et al. [22% adult and 78% pediatric patients (23)] and their respective average body weights (assumed equal to 70 kg and 40 kg, respectively) (Table 1).

The monthly dose of immunoglobulin administered to patients with SID was estimated under the assumption that the entire patient population consists of adults with an average body weight of 70 kg (Table 2). With regard to the frequency of immunoglobulin administration in patients with PID and SID, the study by Cinetto et al. reports a mean interval of cSCIG infusions in patients with PID and SID of 7.48 ± 1.74 days (range 3-15 days) and 7.73 ± 1.75 days (range 5-15 days), respectively, while for patients treated with fSCIG the frequency of administration was 21 days (16). For the purposes of the analysis, a weekly dosing frequency for cSCIG and every three weeks for fSCIG was considered (Tables 1 and 2). With reference to IVIG, a frequency of administration of three weeks was considered, as this is also in line with the SmPC (Tables 1 and 2).

TABLE 1 - Administration schedule and characteristics of infusion by type of immunoglobulin - PID

PID	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)
Frequency of administration	Every 3 weeks	Weekly	Every 3 weeks
No. of administrations/year*	17.3	52	17.3
Average dosage/month	0.31 g/kg	0.31 g/kg	0.31 g/kg
Average dosage/month based on weight**	14.4 g	14.4 g	14.4 g
Maximum infusion volume at the site	600 mL	50 mL	Based off patient's BW
Maximum infusion rate	300 mL/hr/site	35 mL/hr/site***	7.2 mL/kg/hr

* Calculated by comparing 52 weeks for dosing frequency
** Considering 70 kg and 40 kg for adult (22%) and pediatric (78%) patients, respectively
*** If the patient tolerates the initial infusions at the full site dose and maximum speed, an increase in the infusion rate for subsequent administrations can be considered at the patient's discretion and based on the healthcare providers' judgment.

TABLE 2 - Administration schedule and characteristics of infusion by type of immunoglobulin - SID

SID	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)
Frequency of administration	Every 3 weeks	Weekly	Every 3 weeks
No. of administrations/year*	17.3	52	17.3
Average dosage/month	0.25 g/kg	0.25 g/kg	0.25 g/kg
Average dosage/month based on weight**	17.6 g	17.6 g	17.6 g
Maximum infusion volume at the site	600 mL	50 mL	Based off patient's BW
Maximum infusion rate	300 mL/hr/site	35 mL/hr/site***	4.8 mL/kg/hr

* Calculated by comparing 52 weeks for dosing frequency
** Considering 70 kg (100% adults)
*** If the patient tolerates the initial infusions at the full site dose and maximum speed, an increase in the infusion rate for subsequent administrations can be considered at the patient's discretion and based on the healthcare providers' judgment.

With reference to patients with CIDP, since facilitated subcutaneous administration has recently approved for this indication, it was found appropriate to consider the average monthly dosage reported in clinical trials referring to each immunoglobulin. In particular, within the phase 3 ADVANCE-CIDP 3 trial, an open-label extension study of the ADVANCE-CIDP 1 clinical trial aimed at evaluating the efficacy and safety of HyQvia® as maintenance therapy in patients with CIDP, patients were treated with a mean monthly dose of fSCIG of 1.1 g/kg with a maximum dosing frequency of 4 weeks (18) (Table 3).

With reference to cSCIG, in the open-label extension PATH clinical trial evaluating the long-term efficacy and safety of Hizentra® in patients with CIDP, the average weekly dose administered to patients was 0.2 g/kg or 0.4 g/kg (19). An average weekly dose of 0.3 g/kg (19) was therefore considered within the economic model (for a mean monthly dose equal to 1.20 g/kg, Table 3).

Finally, with reference to IVIG, within the PRIMA clinical study, a single-arm open-label phase 3 study aimed at evaluating the efficacy and safety of Privigen® in patients with CIDP, the dose administered was 1 g/kg every 3 weeks (20) (Table 3). The monthly dose of immunoglobulin administered to patients with CIDP was estimated under the assumption that the entire patient population consists of adults with an average body weight of 70 kg.

The cost of subcutaneous administration was obtained from the cost minimization analysis published by Ravasio et al. and aimed at comparing the costs associated with treatment with fSCIG, cSCIG and IVIG in patients with PID and SID in Italy (21). Within the study, the administration cost associated with the single infusion was € 41.25, and it was valued considering the use in a home setting of the infusion pump and the materials (outflows, spikes and syringes) necessary for each individual infusion made available by the hospital. In particular, and in comparison to the other cSCIGs taken into account in the current study, the fSCIG materials and the infusion pump are provided by the company at no additional cost to the hospital. Therefore, for the base case analysis, the administration cost incurred by the NHS for fSCIG was zero.

Finally, the cost of intravenous administration, equal to approximately € 49 per administration, was obtained from a previously published retrospective study conducted on regional administrative databases in order to estimate the consumption of healthcare resources associated with immunoglobulin users (22). The average cost per IVIG administration was estimated considering all visits and tests performed by the patient using immunoglobulins on the day of administration; the valuation of individual healthcare resources was carried out considering the regional reimbursement tariffs.

Since the frequency of administration for some types of immunoglobulins considered within the economic analysis is weekly (cSCIG), for the purpose of calculating the cost of acquiring therapies, the monthly doses were referred to a period of 4 weeks. As a result, the total annual cost of

TABLE 3 - Administration schedule and characteristics of infusion by type of immunoglobulin - CIDP

CIDP	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)
Frequency of administration	Every 4 weeks	Weekly	Every 3 weeks
No. of administrations/year*	13	52	17.3
Average dosage**	1.10 g/kg	1.20 g/kg	1.00 g/kg
Average dosage based on weight***	77.0 g	84.0 g	70.0 g
Maximum infusion volume at the site	600 ml	50 ml	Based off patient's BW
Maximum infusion rate	300 ml/hr/site	35 ml/hr/site****	4.8 ml/kg/hr

* Calculated by comparing 52 weeks for dosing frequency
** Related to 4 weeks (one month) for fSCIG and cSCIG, and to 3 weeks for IVIG
*** Considering 70 kg (100% adults) and related to 4 weeks (one month) for fSCIG and cSCIG and to 3 weeks for IVIG
**** If the patient tolerates the initial infusions at the full site dose and maximum speed, an increase in the infusion rate for subsequent administrations can be considered at the patient's discretion and based on the healthcare providers' judgment.

immunoglobulin acquisition for patients with PID and SID was calculated by multiplying the monthly acquisition cost (referred to 4 weeks) by the number of times that the monthly dose is administered in a year (52/4 = 13 monthly administrations per year). For patients with CIDP, the acquisition cost of cSCIG and fSCIG was calculated as for patients with PID and SID, while the acquisition cost of IVIG was calculated by multiplying the acquisition cost related to three weeks of treatment (as per the PRIMA clinical study) by the number of times in a year that dose is administered every three weeks (52/3 = approximately 17 administrations per year).

The total annual cost of administration was estimated by multiplying the cost of the infusion (subcutaneous or intravenous) by the number of annual administrations calculated, given the frequency of administration for each immunoglobulin.

With reference to the maximum infusion volume and the maximum infusion rate, the data refer to what is reported in the drug's SmPC (Tables 1-3).

Indirect costs

The calculation of indirect costs was carried out considering the days of lost work by the adult patient who has to go to the hospital for the administration of IVIG and considering the lost workdays by the caregiver who accompanies the patient to the hospital for the administration of intravenous immunoglobulins.

For pediatric PID patients, it was considered that IVIG would be carried out in the presence of a caregiver, while for adult patients (with PID, SID or CIDP), in the base-case, it was assumed that 50% of these are accompanied by a caregiver. In particular, as reported above, the percentage of patients with PID aged <18 years obtained from the literature [Lougaris et al. (23)] was 78%, while for patients with SID and CIDP, it was assumed that 100% are aged ≥18 years. These assumptions done for SID and CIDP were based on the literature, which indicates that typical CIDP, although it can occur at any age, is more common in males and most frequently observed between 40 and 60 years of age (5). Similarly, secondary immunodeficiencies are more commonly associated with adult oncohematological neoplasms such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) (2).

The employment rate was estimated considering the number of employed individuals by age group (ISTAT) weighted for resident population (ISTAT) (Table 4); the daily income was obtained from estimates by the INPS Observatory on Employees and Self-Employed Workers (Table 4) considering the annual average income, the total number of working weeks per year and the employment rate coming from ISTAT.

The annual caregiver's and patient's productivity loss was estimated by multiplying the annual number of IVIG administrations by the employment rate and the average daily income for individuals aged 15-89 years.

Scenario analysis

The scenario analysis was conducted in order to assess the economic impact on the results of the base case analysis of the following alternative scenarios:

- cost of subcutaneous administration is also considered for treatment with fSCIG (for all therapeutic indications);
- average dose for fSCIG and cSCIG for the treatment of patients with CIDP taken is equal to the average dose considered for IVIG (intake following the use of cSCIG and fSCIG after stabilization with IVIG);
- 0% and 100% of adult patients go to the hospital for the administration of intravenous immunoglobulin accompanied by a caregiver (versus 50% assumed in the base-case);
- maximum and minimum value of the average monthly dosage for patients with PID and SID (based on the standard deviation observed in Cinetto et al.).

Results

The model estimated an average annual cost for the treatment of PID patients treated with fSCIG, cSCIG and IVIG of € 12,190, € 14,336 and € 13,789, respectively (Table 5, Fig. 1). In particular, with reference to the treatment with fSCIG, the cost is associated only with the acquisition cost as the infusion

TABLE 4 - Estimation of indirect costs associated with patients with PID, SID and CIDP

	PID	SID	CIDP	Sources
Share of patients aged <18 years	78%	0.0%	0%	PID: (23)
Share of patients aged ≥18 years	22%	100.0%	100%	SID and CIDP: assumption
Employment rate 15-89 years old	46.4%	46.4%	46.4%	ISTAT (24)
Patient Daily Income	83.6 €	83.6 €	83.6 €	INPS Observatory on employees and self-employed workers (25)
Caregiver Daily Income	83.6 €	83.6 €	83.6 €	ISTAT (24) and INPS Observatory on Employees and Self-Employed Workers (25)
N° IV administrations/year	17.3	17.3	17.3	–
Loss of annual patient productivity per IV administration	148.7 €	672.0 €	672.0 €	–
Loss of annual caregiver productivity for IV administration (patients with < 18 years of age)	523.2 €	0.0 €	0.0 €	–
Loss of annual caregiver productivity for IV administration (patients with ≥ 18 years of age)	74.4 €	336.0 €	336.0 €	–
Total annual indirect cost per patient	746.3 €	1,008.0 €	1,008.0 €	–

pump and ancillary materials (such as flushes, spikes and syringes) are provided by the company; additionally there are no administration costs borne by the hospital, especially because we have focused the analysis only to the maintenance phase of the therapy (so the first administration done in hospital including the training for SCIG self-administration was not considered). Moreover, since it is a therapy that can be administered in a home setting, the indirect costs evaluated in terms of loss of productivity due to the disease are absent. For cSCIG and IVIG treatment, 15% and 6.2% of the total cost are associated with the administration cost, respectively, while with respect to IVIG treatment, 5.4% of the total cost corresponds to the indirect costs associated with intravenous administration. With reference to the patient with SID, the model estimated a total cost associated with treatment with fSCIG, cSCIG and IVIG of € 14,902, € 17,047 and € 16,762, respectively (Table 5, Fig. 2). Also in this case, the administration cost for fSCIG is absent, while it is equal to 12.6% and 5.1%, respectively for patients treated with cSCIG and IVIG. Compared to indirect costs, the loss of productivity associated with intravenous infusion treatment in patients with SID was 6% of the total annual cost. Finally, with reference to the patient with CIDP, the model estimated an average annual total cost associated with treatment with fSCIG, cSCIG and IVIG of € 65,065, € 73,125 and € 80,727, respectively (Table 5, Fig. 3). For these patients, the average annual cost associated with administration was 2.9% and 1.1% for patients treated with cSCIG and IVIG (absent for fSCIG treatment), respectively, while the annual indirect costs associated with intravenous administration were 1.2% of the total cost.

The model suggests that the use of fSCIG treatment in patients with PID would therefore result in a reduction in annual social expenditure per patient (direct and indirect costs) of approximately € 2,145 and € 1,599 respectively in comparison with cSCIG and IVIG, while in patients with SID, it would result in a reduction in social expenditure per patient equal to approximately € 2,145 and € 1,860 respectively in comparison with cSCIG and IVIG. With regard to patients with CIDP, the use of fSCIG treatment would result in a reduction in social expenditure per patient of € 8,060 and € 15,662, respectively, in comparison with cSCIG and IVIG. The scenario analysis confirms the economic savings deriving from the use of immunoglobulin with facilitated subcutaneous administration (Table 6).

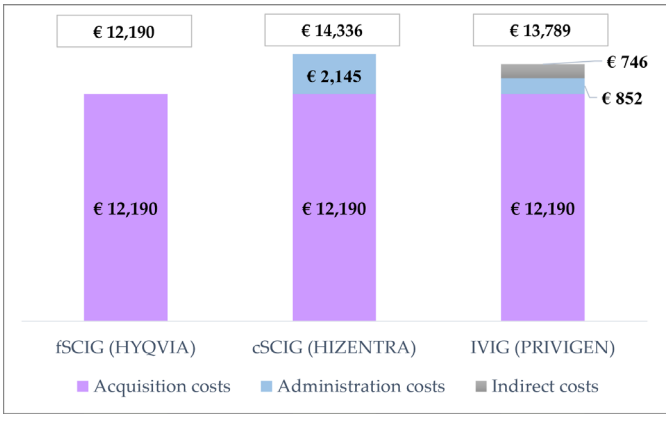

FIGURE 1 - Total annual cost and per cost item for treating patients with PID.

TABLE 5 - Average annual costs by type of immunoglobulin

	PID			SID			CIDP		
	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)	fSCIG (HYQVIA)	cSCIG (HIZENTRA)	IVIG (PRIVIGEN)
Annual acquisition cost	€ 12,190	€ 12,190	€ 12,190	€ 14,902	€ 14,902	€ 14,902	€ 65,065	€ 70,980	€ 78,867
Annual cost of administration	€ 0	€ 2,145	€ 852	€ 0	€ 2,145	€ 852	€ 0	€ 2,145	€ 852
Annual indirect costs	€ 0	€ 0	€ 746	€ 0	€ 0,00	€ 1,008	€ 0	€ 0	€ 1,008
Total annual cost	€ 12,190	€ 14,336	€ 13,789	€ 14,902	€ 17,047	€ 16,762	€ 65,065	€ 73,125	€ 80,727
Delta HYQVIA vs others		–€ 2,145	–€ 1,599		–€ 2,145	–€ 1,860		–€ 8,060	–€ 15,662

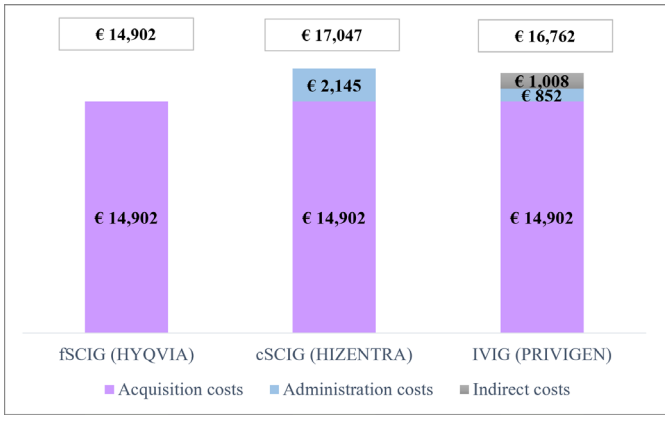

FIGURE 2 - Total annual cost per cost item for treating patients with SID.

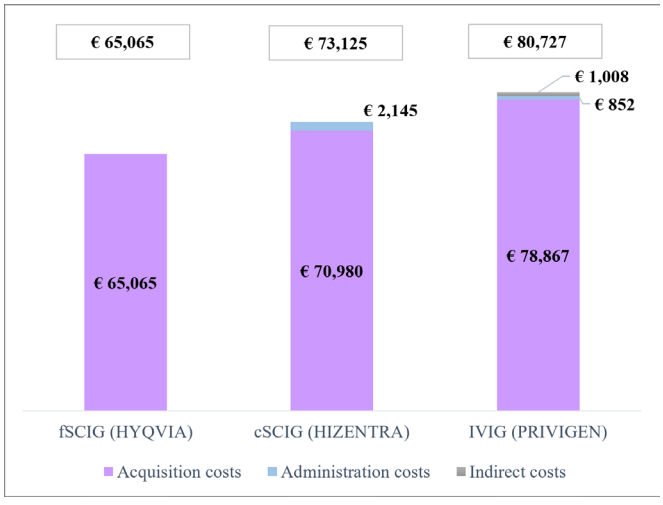

FIGURE 3 - Total annual cost and per cost item for treating patients with CIDP.

Discussion

The study attempted to estimate, from a social perspective, the annual cost associated with the treatment of patients with PID, SID and CIDP relative to the national context. The model used for this analysis showed that treatment with facilitated subcutaneous immunoglobulin is associated with a reduction in social spending. In particular, with reference to patients with PID and SID, assuming an identical acquisition cost between the different therapies, the analysis suggests a potential reduction in the administration cost and indirect costs with the use of fSCIG compared to conventional subcutaneous immunoglobulin and intravenous administration. Additionally, the estimated annual productivity loss for intravenous infusion is greater in patients with SID and CIDP since, based on published literature, the mean age of patients with SID and CIDP is approximately 61 and 57 years, respectively (26-29); therefore, on average, a patient with SID or CIDP is of working age. However, as the mean age reported in published studies indicates that a proportion of patients are older than 65 years, and therefore, they are associated with a lower employment rate, for the calculation of indirect costs, the model considers the employment rate for individuals aged 18-89 to account for age-related differences in productivity. National registries of primary immunodeficiencies show that 78% of patients are <18 years (23), so the loss of productivity associated with the patient with PID is lower than that estimated for patients with SID and CIDP.

With reference to patients with CIDP, considering the dosage reported in the clinical trials relating to each type of immunoglobulin for the calculation of the cost of acquiring drug therapy, the use of fSCIG would also lead to a reduction in the cost of acquiring treatment.

With reference to the comparison between the administration of immunoglobulins subcutaneously and intravenously, some recent studies conducted at the European level, in particular in Switzerland and France, have shown that treatment with SCIG is associated with savings for the health system compared

to treatment with IVIG. In particular, the cost minimization analysis conducted by Perraudin et al. (Switzerland) according to a social perspective estimated a higher cost relative to 48 weeks of treatment with IVIG compared to SCIG in patients with CIDP (8). This study considered the dosage reported in the SmPC to be 1 g/kg every 3 weeks for IVIG and 0.4 g/kg per week in the initial phase and 0.2 g/kg per week for the maintenance phase for SCIG. The authors report that the greatest cost driver was associated with immunoglobulin doses.

The study conducted by Lepage et al. (France) in order to evaluate and compare the cost of IVIG and SCIG treatment in patients with CIDP according to a social perspective and a time horizon of 5 years estimated an annual cost per patient treated with IVIG equal to € 70,203 and a cost per patient treated with SCIG equal to € 63,346 (9); this study also estimated a potential 5-year savings associated with the introduction of SCIG treatment in patients with CIDP of approximately € 8.1 million. In the study conducted for the French context, the posology and frequency of administration of immunoglobulins were obtained from the respective SmPCs. The authors report that the cost of hospitalizations and the annual number of administrations associated with IVIG treatment were the parameters associated with the greatest impact on outcomes.

With regard to the national context, the cost minimization analysis conducted by Cocito et al. by administering a questionnaire to 5 patients with CIDP and 5 patients with multifocal motor neuropathy who had previously received treatment with IVIG for at least 6 months, compared the costs associated with treatment with SCIG and IVIG according to the perspective of the National Health Service (30). Because these patients responded to immunoglobulin treatment and were clinically stable, the monthly dose of SCIG was considered equivalent to that previously administered during IVIG therapy for each patient and was considered to be 1 g/kg. This study estimated an annual cost per patient of € 42,772 and € 43,456, respectively, for treatment with SCIG and IVIG; the savings deriving from the use of treatment with SCIG were associated with the absence of adverse events and the absence of medical personnel for administration.

Also at the national level, the cost minimization analysis conducted by Lazzaro et al. aimed at comparing the costs associated with treatment with SCIG and IVIG in patients with CIDP according to the social perspective and considering a time horizon of one year estimated an annual cost per patient treated with SCIG and IVIG, respectively, equal to € 49,535 and € 50,896 (10). In this study, the average monthly dosage was 1 g/kg for both treatments, and again, the higher cost driver was associated with the cost of acquiring immunoglobulins.

The study by Piscitelli et al., it is the only one that reports discordant data with respect to the published literature (31). The analysis was conducted from a social perspective and through the use of data collected on 12 patients with CIDP referred to the neurophysiopathology unit at the "Antonio Cardarelli" hospital who switched to home treatment with SCIG after previous treatment with IVIG and who were neurologically stable one year after the switch. The divergence of the results from what was previously reported in the literature depends on the price/gram higher considered for the SCIG (€48 for Hizentra and €51.57 for Hyqvia) compared to IVIG (€30.97); however, since immunoglobulin prices are currently aligned, the difference in acquisition costs of the three different administration types may depend solely on their dosage and not on the price.

Finally, the cost minimization analysis recently conducted by Ravasio for the comparison of treatment with SCIG and IVIG in patients with PID and SID according to the hospital's perspective, showed that treatment with fSCIG is the most cost-saving for both indications (PID: HyQvia €20,020, Hizentra €22,165 and Venital €24,968; SID: HyQvia € 17,160, Venital € 22,108) (21). In this study, the average monthly dose administered to patients was considered the same for all types of immunoglobulins considered in the analysis and was taken at 28 g and 24 g respectively, for patients with PID and SID, assuming an average patient weight of 70 kg.

Like all economic models that attempt to reconstruct and synthesize the management and treatment path of patients suffering from a given condition in order to estimate its costs, the analysis reported here has limitations. Firstly, the monthly doses considered for PID and SID refer to the findings of the recently published literature referring to observational studies. This choice was made in order to consider what happens in clinical practice with respect to the treatment of pathological conditions for which immunoglobulins with facilitated subcutaneous administration have been authorized and used for many years now. In particular, for the purpose of this analysis, the average monthly dose observed in clinical practice was used, which is subject to high variability, as also demonstrated by the standard deviation reported in the study by Cinetto et al. (309.31 ± 95.33 mg/kg for PID, 251.94 ± 82.20 mg/kg for SID) (16). Because the cost of treatment is influenced by the dose taken, the impact of this parameter was assessed in the scenario analysis by considering the standard deviation reported by Cinetto et al. A further limitation refers to the use of the monthly doses administered to patients with CIDP observed within the respective clinical trials, because at the time of the analysis, there are no data available from observational studies about the monthly doses consumed by patients with CIDP. Since in most cases subcutaneous immunoglobulin is prescribed following stabilization treatment with intravenous immunoglobulin, it was appropriate to conduct a scenario analysis in order to assess the potential economic impact of using the same dose for all types of immunoglobulin under analysis; in particular, since the same dose previously administered with intravenous treatment is usually maintained for patients who switch to subcutaneous immunoglobulin treatment, the same dose observed in the clinical study conducted for Privigen was considered in the scenario analysis for HyQvia and Hizentra.

With reference to the other cost items considered within the economic analysis, further limits refer to the assumptions that have been made with reference to the estimation of indirect costs. In particular, for the estimation of these costs, it has been assumed that 50% of adult patients go to the hospital for the administration of intravenous immunoglobulin accompanied by a caregiver. The scenario analysis conducted considering that 0% of adult patients attend the hospital

TABLE 6 - Scenario analysis

PID	**cSCIG (HIZENTRA)**	**IVIG (PRIVIGEN)**
Delta HYQVIA vs others (base-case)	–€ 2,145	–€ 1,599
Delta HYQVIA vs others (inclusion of cost of fSCIG administration)	–€ 1,430	–€ 884
Delta HYQVIA vs others ([0%; 100%] of adult patients go to hospital for IVG administration with a caregiver)	As base-case	[–€ 1,524; –€ 1,673]
Delta HYQVIA vs others (change in average monthly dosage for patients with PID and SID based on standard deviation observed in Cinetto et al.)	As base-case	As base-case
SID	**cSCIG (HIZENTRA)**	**IVIG (PRIVIGEN)**
Delta HYQVIA vs others (base-case)	–€ 2,145	–€ 1,860
Delta HYQVIA vs others (inclusion of cost of fSCIG administration)	–€ 1,430	–€ 1,145
Delta HYQVIA vs others ([0%; 100%] of adult patients go to hospital for IVG administration with a caregiver)	As base-case	[–€ 1,524; –€ 2,196]
Delta HYQVIA vs others (change in average monthly dosage for patients with PID and SID based on standard deviation observed in Cinetto et al.)	As base-case	As base-case
CIDP	**cSCIG (HIZENTRA)**	**IVIG (PRIVIGEN)**
DeltaHYQVIA vs others (base-case)	–€ 8,060	–€ 15,662
Delta HYQVIA vs others (inclusion of cost of fSCIG administration)	–€ 7,524	–€ 15,126
Delta HYQVIA vs others (dose for IVIG also taken for fSCIG and cSCIG)	–€ 2,145	–€ 1,860
Delta HYQVIA vs others (dose for IVIG also taken for fSCIG and cSCIG, and inclusion of cost of fSCIG administration)	–€ 1,430	–€ 1,145
Delta HYQVIA vs others ([0%; 100%] of adult patients go to hospital for IVG administration with a caregiver)	As base-case	[–€ 15,326; –€ 15,998]

for IVG administration accompanied by a caregiver showed that the reduction in annual social expenditure per patient associated with the use of fSCIG estimated in the base case decrease of about 4,7%, 18.1% and 2.1% for PID, SID and CIDP respectively, however it is still economically advantageous compared to IVIG. In addition, consistent with what is reported in the literature (2,5), the absence of patients aged ≤18 years was assumed for the analysis conducted for patients with SID and CIDP.

With reference to the estimation of the cost of intravenous administration, the study obtained from the literature used to estimate this cost considered, in addition to the cost specifically relating to the intravenous infusion provided for by the national tariff list, also the cost relating to the examinations and visits that the patient carries out on the same day as he goes to the hospital for administration. Regarding administration cost considered for subcutaneous administration, if the monthly dosage were the same for cSCIG and fSCIG (as assumed for PID and SID in this analysis) and administration materials were provided by the manufacturer also for cSCIG, the advantage of using fSCIG would be in terms of quality of life due to the lower number of administrations, as the cost would remain the same between the two alternatives. Additionally, the transport costs incurred by the patient who goes to the hospital for intravenous administration were not considered within the analysis. The exclusion of these costs was considered appropriate as there was insufficient information available to generate an estimate that could have considered the high variability associated with this expense item. Finally, the analysis used the ex-factory prices reported in the respective Official Journals for each immunoglobulin (13-15), as in Italy, all immunoglobulins share the same ex-factory price, with no confidential discounts applied. It should be noted, however, that regional confidential agreements exist, but they cannot be referenced.

Although it is acknowledged that the results may be affected by variability, particularly in the dosing regimens used in clinical practice, we believe that this analysis can provide decision-makers with valuable insights into the potential impact of different formulations of immunoglobulins on both direct and societal costs.

Conclusions

The use of immunoglobulin treatment with facilitated subcutaneous administration for patients with PID, SID, and CIDP, in addition to potential advantages in terms of frequency and speed of administration, might allow a reduction in the direct and indirect costs associated with the treatment of these patients, suggesting it is a cost-saving option compared to cSCIG and IVIG alternatives.

Disclosures

Conflict of interest: Ripoli S, Fioravanti L and Papa C are employees of Takeda and hold stock or stock options in Takeda. Bini C, Scortichini M and Sciattella P declare that they have no conflicts of interest.

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