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ORIGINAL ARTICLE

Surveillance study on the tolerability and safety of Flebogamma® DIF (10% and 5% intravenous immunoglobulin) in adult and pediatric patients

Laia Alsina[1], Andreas Mohr[2], Maria Montañés[3], Xènia Oliver[3], Esperanza Martín[4], Jaime Pons[5], Elizabeth Drewe[6], Jens Papke[7], Georg Günther[8], Ronnie Chee[9], Mark Gompels[10] & the investigators of the Flebogamma DIF PASS Study Group

[1]Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Passeig de Sant, Joan de Déu 2, 08950 Esplugues de Llobregat, Barcelona, Spain
[2]Hematology and Oncology, OncoResearch Lerchenfeld, Lerchenfeld 14, 22081 Hamburg, Germany
[3]Pharmacovigilance Department, Instituto Grifols S.A., Avinguda de la Generalitat 152-158, 08174 Sant Cugat del Vallès, Barcelona, Spain
[4]Pneumology Service, Hospital Sant Joan de Déu, Fundació Althaia. Carrer Dr. Joan Soler, s/n, 08243 Manresa, Spain
[5]Immunology Service, Hospital Son Espases, Carrer de Valldemossa 79, 07120 Palma de Mallorca, Spain
[6]Clinical Immunology and Allergy Department, Nottingham University Hospitals - QMC Campus, Hucknall Road, Nottingham NG5 1PB, UK
[7]Practice and Day Clinic for Internal Medicine and Oncology, Rosa-Luxemburg-Straße 6, 01844 Neustadt in Sachsen, Germany
[8]Medical Healthcare Centre for Blood and Cancer Diseases, Kurfürstenstraße 20, D-14467 Potsdam, Germany
[9]Clinical Immunology Department, Royal Free London NHS Foundation Trust, 17 Lyndhurst Gardens, London NW3 5NU, UK
[10]Immunology and Allergy Department, Southmead Hospital, Dorian Way, Westbury-on-Trym, Bristol BS10 5NB, UK

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Correspondence
Laia Alsina, Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Passeig de Sant Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain. Tel: +34 932804000, ext. 71709; Fax: +34 932033959; E-mail: lalsina@hsjdbcn.org

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Abstract

Direct comparisons of tolerability and safety of concentrated intravenous immunoglobulin (IVIG) versus less concentrated products are scarce. In this postauthorization, prospective, observational, multicenter study, a systematic comparison of 10% and 5% concentrations of Flebogamma® DIF IVIG was performed in both adult and pediatric patients treated with the studied IVIG products according to the approved indications under routine conditions. Dose of product administered, adverse events (AEs), physical assessments, laboratory tests, and concomitant therapy were analyzed. Patient recruitment in the 10% and 5% product groups was, respectively, 34 (32 analyzed, 13 of them children, receiving 130 IVIG infusions) and 35 (34 analyzed, receiving 135 IVIG infusions). Twenty-four infusions (18.5%; 95% CI: 11.8, 25.1) with the 10% product and 3 (2.2%; 95% CI: −0.3, 4.7) with the 5% product were associated with potentially treatment-related AEs ($P < 0.0001$). Nine patients (28.1%) infused with the 10% product and 3 (8.8%) infused with the 5% product presented, respectively, 33 and 8 treatment-related AEs (of which 7 and 6, respectively, were serious AEs, experienced by only three hypersensitive patients). The profile of AEs occurring with the infusion of 10% and 5% products were comparable. The most frequent treatment-related AEs were headache ($n = 17$, 3 patients; 15 episodes, 1 patient) and pyrexia ($n = 6$, 4 patients). In conclusion, no unpredictable risk was detected for both Flebogamma DIF 10% and 5% concentrations, which were therefore deemed as safe and well-tolerated IVIG in the studied population. The frequency of infusions associated with treatment-related AEs was lower with the 5% concentration.

Introduction

Over the past few decades, the use of intravenous immunoglobulin (IVIG) in a diverse range of immunodeficiency, inflammatory, and infectious disorders has increased significantly (Orange et al. 2006). Newer processes for manufacturing IVIG products have increased the yield of intact IgG molecules and have also

improved their tolerability and safety (Stein 2010). However, these different manufacturing processes make nonequivalent plasma-derived products, and the final composition of IVIG products has resulted in varying tolerability profiles (Marzo et al. 2011). Tolerability is mainly based on product characteristics such as formulation, concentration, osmolality, IgA content, and pH. Therefore, as it is known for plasma-derived products, different IVIG are not interchangeable even assuming bioequivalence (FDA, 2001; EMEA, 2009). Patients receiving IVIG products should be carefully monitored at the initial administration or when they are switched from one product to another (Ballow 2005).

In general, administration, especially infusion rate and dose, should be done in accordance with the Summary of Product Characteristics (SPC). Although IVIG administration is generally considered a safe and well-tolerated therapy, adverse events (AEs) may appear at any time, usually within the first hour after the start of the infusion. Slowing the infusion rate or switching to another product are common measures to eliminate or alleviate them (Orbach et al. 2005). Nevertheless, some patients will still experience significant AEs during the infusion, and these are more commonly late AEs (late in an infusion or hours after the end of an infusion). Generally, mild, transient AEs such as headache, nausea, vomiting, or back pain are expected after treatment with IVIG (Orbach et al. 2005). Serious, but rare, AEs have also been reported including hypersensitivity, aseptic meningitis syndrome, acute renal failure, thromboembolism, and hemolytic anemia (Orbach et al. 2005).

Flebogamma® dual inactivation and filtration (DIF) is a highly purified, unmodified human IgG product for intravenous administration, manufactured by Grifols. It is currently licensed in Europe, the United States, and over 25 other countries around the world (SPC, 2009). Flebogamma DIF is available in 5 and 10 mg/mL (5% and 10%) IgG concentrations. The volume of the 10% solution is half than that for the 5% solution, which allows shorter infusion time and may thus improve patients' quality of life.

Results from previous studies in patients with primary immunodeficiencies (PID) and immune-mediated idiopathic thrombocytopenic purpura (ITP) have shown that Flebogamma DIF 5% and 10% are safe and effective for the treatment of these conditions (Berger and Pinciaro 2004; Ballow 2009, 2013; Julia et al. 2009; Berger et al. 2010). However, the rate of infusions associated with potentially related AEs was higher with Flebogamma DIF 10% than with the lower concentration Flebogamma DIF 5%. Although the occurrence of higher rates of AEs associated with more concentrated IVIG products is addressed in the literature (Orbach et al. 2005; Carbone 2007; Bonilla 2008; Chérin and Cabane 2010), direct comparisons with the less concentrated product are limited. For example, differences in trial design, patient population, dosage, frequency, and maximum rate of administration, AE definition criteria, use of premedication to alleviate the AEs, etc., confound direct comparisons among separate published studies for each concentration. In addition, there is not enough data to support whether serious, but less common AEs occur at a higher frequency with concentrated IVIG products.

Therefore, a postauthorization, surveillance study was carried out to prospectively assess in routine clinical practice the tolerability, safety, and rate of potential infusion-related AEs, of Flebogamma DIF 10%, compared with the same product at lower concentration, Flebogamma DIF 5%.

Methods

Study design

This was a postauthorization, prospective, observational, nonrandomized/nonstratified, open-label, multicenter safety study of Flebogamma DIF 5% and 10% (Instituto Grifols SA, Barcelona, Spain) performed at 19 centers in Spain, United Kingdom, and Germany. The rights and welfare of all patients were adequately protected. This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and approved by the Ethics Committees of the respective sites if required by local rules.

The study was designed to be consistent with the clinical routine practice and conditions specified in the SPC; therefore, all treatments were performed following the local investigator protocols. Because this is a nonrandomized, noncontrolled, observational study, there was no specific assignment of patients to treatment groups. However, the number of patients included was balanced between the 5% and 10% treatment groups.

Each patient was enrolled in the study after fulfilling the inclusion and exclusion criteria and having signed a written informed consent. Patients were assigned identifying numbers in a numeric order per center which were entered in the electronic Case Report Form (eCRF) and in the confidential patient identification list by the investigators.

Study products

Flebogamma DIF is a highly purified, unmodified human IgG manufactured from plasma donated by healthy donors for intravenous administration at concentrations of 50 or 100 mg/mL, named as Flebogamma DIF 5% and Flebogamma DIF 10%, respectively.

Flebogamma DIF 5% contains 2.5 g human normal immunoglobulin and 2.5 g D-sorbitol (as stabilizer) in 50 mL of water for injection. IgG purity reaches at least 97%. The percentages of IgG subclasses are approximately 66.6% IgG1, 27.9% IgG2, 3.0% IgG3, and 2.5% IgG4. It contains trace amounts of IgA below the detection limit (lower than 0.1 mg/ml) (SPC, 2009; Ballow et al. 2011). Flebogamma DIF 10% contains 5 g human normal immunoglobulin and 2.5 g D-sorbitol (as stabilizer) in 50 mL of water for injection. IgG purity reaches 99.6 ± 0.4. The manufacturing process of Flebogamma DIF includes safety steps such as a solvent–detergent treatment and sequential nanofiltration through filters with pore sizes of 35 and 20 nm as extra viral elimination steps, in addition to the pasteurization (Caballero et al. 2010; Diez et al. 2010; Jose et al. 2013). Both Flebogamma DIF 5% and 10% share the same fractionation and purification phases. The product concentration is then adjusted to either 5% or 10%.

Patient selection

Male or female patients, 2 years of age or older, treated with Flebogamma DIF 10% or 5% for approved indications (SPC, 2009) could be enrolled at the discretion of the treating physician.

Patients were excluded if any of the following exclusion criteria were met: the subject was known to have a history of intolerance to any Flebogamma DIF-containing substances; to have a history of anaphylactic reactions to blood or blood components; diagnosed with IgA deficiency and had anti-IgA antibodies; was participating in another clinical study involving an investigational treatment or had participated within the past 4 weeks; the subject was unlikely to adhere to the protocol requirements of the study.

Study objectives

The primary objective of this study was to prospectively assess the safety and tolerability of Flebogamma DIF 10% in the clinical practice under routine conditions by comparing potentially related AEs between products 10% and 5%.

The principal safety endpoint was the number of infusions with potentially related AEs relative to the total number of infusions. Secondary safety endpoints included frequency and type of AEs potentially related to study products and frequency of patients experiencing AEs or clinically significant changes in vital signs and laboratory parameters. Tolerability endpoints included frequency of serious and severe AEs potentially related to study products.

Procedures and variables collected

Administration of Flebogamma DIF 10% and Flebogamma DIF 5% was done in accordance with the SPC. AEs may appear at any time and measures to avoid or alleviate them could be taken, including premedication and slowing the infusion rate. The dose of the Flebogamma DIF product administered to each subject was recorded in the eCRF, as well as the lot number for each vial. AEs and potentially treatment-related AEs, vital signs, physical assessments, and laboratory tests, including renal function (creatinine levels) and viral status (hepatitis A, B, and C, and HIV) and any concomitant therapy were listed and tabulated.

All AEs that began during or up to 72 h after an infusion were classified by system organ class (SOC) and preferred term (PT) according to the MedDRA dictionary (Version 17.0), and analyzed. The following information was included: type, seriousness ("serious" [SAE], "nonserious"), and severity ("severe," "moderate," "mild") of the event; clinical course leading up to the event; relevant laboratory measurements; whether the treatment was stopped and when; measures taken; postmortem findings; and an opinion on causality. AEs potentially related to study products were assessed by the treating physician as "doubtful," "possible," "probable," or "definitely." Abnormal vital signs and clinical laboratory assessment that worsened from baseline, and considered by the local investigator to be clinically significant, were reported as an AE/SAE if it met the definitions. Safety evaluation included monitoring of short-term tolerance (blood pressure, heart rate, respiratory rate, temperature).

Statistical analysis

Previous data from clinical trials performed with Flebogamma DIF at 10% and 5% concentrations showed a frequency of infusions with potentially related AEs, relative to the number of infusions, of 30.5% and 10.8%, respectively (Berger 2007; Ballow 2009; Julia et al. 2009; Berger et al. 2010). Therefore, to ensure more than 90% power using a one-sided test with a significance level of 0.01, an effective sample size of at least 102 infusions per group was needed to detect a difference of 20% in the rates of both concentrations (sample size for the comparison of two independent proportions with Z test). Therefore, taking into account the expected number of infusions per patient, a total of 60–70 patients had to be recruited.

All subjects that received at least one infusion of Flebogamma DIF 10% or 5% during the study were included in the analysis. Descriptive statistics for continuous variables included mean, standard deviation (SD),

95% confidence interval (CI), median, and interquartile range (Q1, Q3). For categorical variables, summary measures were counts (n) and percentages (%). Quantitative variables were compared between groups by means of a Student's t test. Wilcoxon signed-rank test was used instead of a regular Student's t test when comparing two related or matched samples. Categorical data variables were compared by means of the chi-squared test or, in variables with reduced/limited sample size, by means of the Fisher's exact test. To avoid missing outlier results, all statistical tests were two sided and were performed using a 5% significance level. Furthermore, for the primary endpoint, the statistical test was two sided and was performed using a 2% significance level. No adjustment for multiple comparisons or corrections for multiplicity were planned and missing data were not imputed. The SAS v. 9.2 (or later version) program was the statistical software used.

Results

Patient population

Sixty-nine patients from 19 centers recruited from August 2011 until August 2014 were included in the study. The final analysis of the study included 66 patients (13 of them children 2–15 years old, all of them allocated to the 10% product group); flow of patients through the study is shown in Figure 1. Three subjects did not receive any infusions and were therefore excluded: two patients in the 10% group because their treatment was not in accordance with approved product labeling (follicular lymphoma and Hodgkin lymphoma), and one patient in the 5% group because the recruitment period was over.

Ten patients, 2 in the 10% product group and 8 in the 5% product group did not complete the study (Fig. 1). Two of the patients were discontinued for administrative reasons: one because of the inability to deliver the IVIG product to the center, and one because of the center withdrawing from the study. One patient discontinued because of being treated for myasthenia gravis (not an approved IVIG indication). One death was reported during the study due to elective hip surgery with lethal complication of pulmonary edema, with no relationship with the study medication. The two cases of allergic reaction were defined as AEs.

Detailed demographic and clinical characteristics of subjects are summarized in Table 1. Of the 66 eligible patients analyzed, 56 patients presented PID or secondary immunodeficiency (SID) disease. Eight patients had ITP, two patients suffered Guillain–Barré syndrome (GBS), and one patient was treated for Kawasaki disease (KD). The most frequent concomitant medications were systemic antibiotics, followed by analgesics, systemic antivirals, and antacids.

Infusions

The total number of infusions in the study was 265 (130 in the 10% product group and 135 in the 5% product group), of which six were not successfully completed due to AEs (4 in the 10% product group and 2 in the 5% product group). Details of the mean number of infusions per patient and mean IVIG dose infused are shown in Table 1. Regarding type of disease, the mean replacement IVIG dose infused for PID/SID was 321 ± 170 mg/kg (234 infusions), while for autoimmune diseases (ITP, GBS, and KD) the mean dose was 743 ± 446 mg/kg (31 infusions). Twenty-seven (20.8%) and 28 (20.7%) infusions with the 10% and 5% products, respectively, used premedication to avoid adverse events: antihistaminics (11 infusions in 8 patients), glucocorticoids (35 infusions in 7 patients), analgesics (acetaminophen, 2 infusions in 2 patients), and glucose solution for headache (10 infusions in 2 patients).

The mean dose of IVIG prior to enrolling in the study was 322 ± 237 mg/kg in adults and 367 ± 102 mg/kg in children (median time: 85 days; range: 1 day–15 years). The number of naïve and pre-exposed patients are shown in Table 1.

Safety assessments

Overall, 27 infusions of the total of 265 (10.2%; 95% CI: 6.6, 13.8) received by 12 patients (6 children) were associated with AEs potentially related to study products (main endpoint of the study): 24 infusions (18.5%; 95% CI: 11.8, 25.1) with the 10% product and 3 infusions (2.2%; 95% CI: −0.3, 4.7) with the 5% product ($P < 0.0001$). Rates of AEs per infusion were 31.5% (41/130) with 10% product and 18.5% (25/135) with 5% product. Details on the seriousness and severity as rated by the investigator are summarized in Table 2.

The number of AEs classified by SOC and PT is displayed in Table 3. It should be noted that 15 of the 17 headache episodes (all of them mild) occurred in the same patient, one in each of the 15 infusions he received. This patient was previously exposed to Flebogamma DIF and was treated with 100 mL of glucosade solution 5% in 10 occasions for headache prevention. The six pyrexia episodes occurred in four patients, two of them experienced two episodes in two respective infusions (although one of the pyrexia episodes was recorded three times during the same infusion, it was actually a single AE).

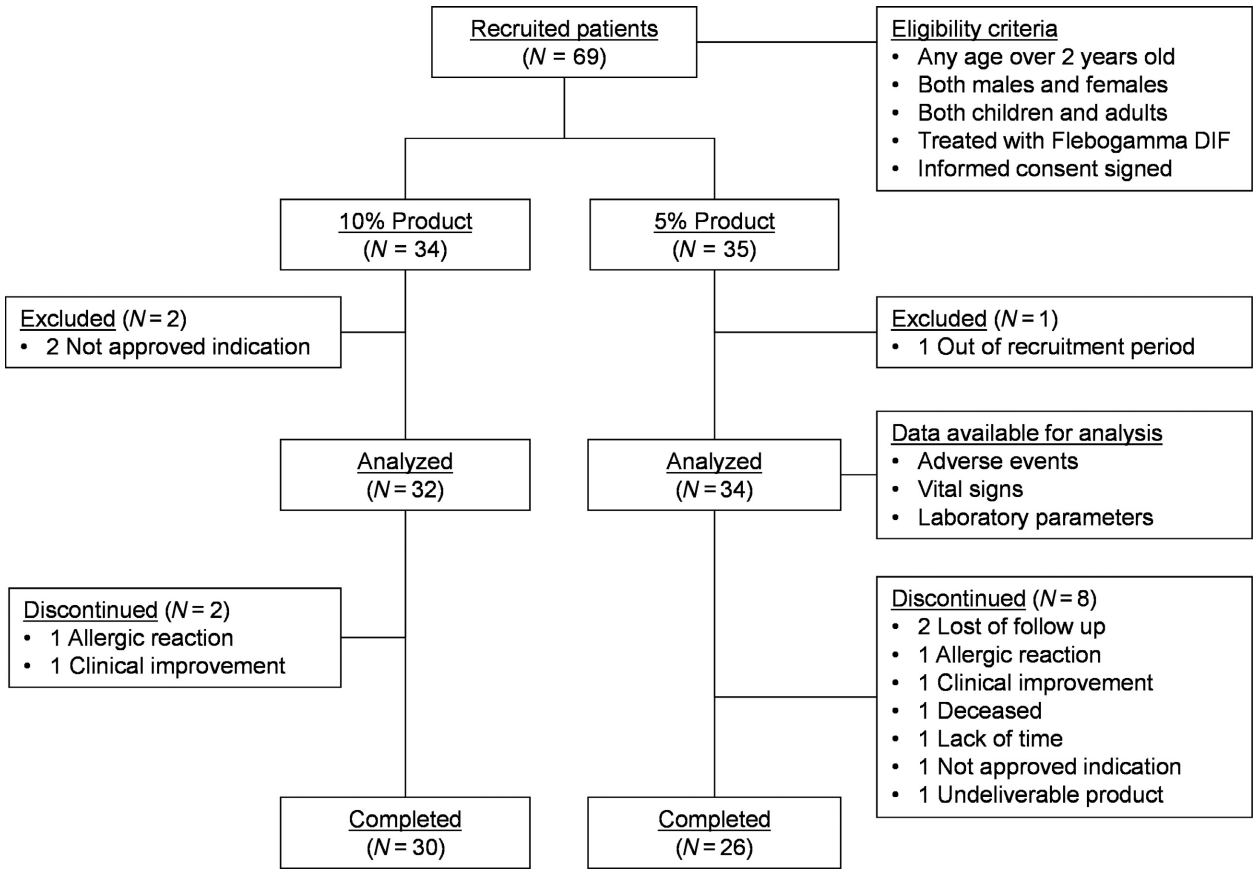

Figure 1. Flowchart of patients through the study.

Twelve of the 28 naïve patients (42.9%) experienced AEs, some more than patients previously exposed to any IVIG (9/38 patients; 23.7%) or previously exposed to only Flebogamma DIF (6/30 patients; 20.0%). A similar pattern was observed regarding AEs potentially related to the study products (percentages: 25.0%, 13.2%, and 10.0%, respectively). Differences were statistically nonsignificant in all cases.

Of the SAEs ($n = 17$) experienced by the patients (Table 3), 13 were potentially related to treatment, all of them grouped in three allergic reactions observed in three adult patients (two cases occurred during and after the infusion of 10% product, respectively, the first was rated moderate in severity while the second was unrated; and one case occurred during the 5% product infusion and was rated moderate in severity). Additional SAEs associated with the hypersensitivity event were recorded during the infusion with the 5% product and during one of the infusions with the 10% product: 2 chills, 2 dyspnea, 2 chest pain, 2 increased blood pressure, 1 impairment of the patient's general condition, and 1 actinic keratosis. In the three cases of allergic reaction, the product was discontinued. All SAEs related to treatment resolved.

As displayed in Figure 2, 29 of the 43 potentially treatment-related AEs (67.4% of all potentially treatment-related AEs) were experienced by only three patients (4.5% of all patients), 2 in the 10% product group, and 1 in the 5% product group, all of them adults. Similarly, the 13 SAEs were experienced by only three patients, associated with three allergic reactions, as described above. Of the eight children with high IVIG dose (autoimmune disease), 4 (50.0%) experienced at least one treatment-related AEs, a percentage not markedly different than the 40.0% (2 of 5 children) observed in low IVIG dose (immunodeficiency). All 13 children were in the 10% product group (the six children experiencing treatment-related AEs represented the 46.2%; Fig. 2). In adults, 3 (15.8%) of 19 treated with 10% product and 3 (8.8%) of 34 treated with 5% product experienced at least one treatment-related AEs. None of the three adults with autoimmune disease (all of them in the 5% product group) experienced treatment-related AEs (Fig. 2).

Vital signs and laboratory mean values were overall within normal ranges during the study. No changes in viral markers were observed.

Table 1. Demographic, anthropometric, and medical data of the analyzed patients.

	Flebogamma DIF 10% (*N* = 32)	Flebogamma DIF 5% (*N* = 34)	Overall population (*N* = 66)
Sex, male (*n* [%])	15 (46.9)	22 (64.7)	37 (56.1)
Children (*n* [%])	13 (40.6)	0	13 (19.7)
Age adults (years, median [Q1, Q3])	59 (46, 73)	62 (47, 69)	62 (46–70)
Age children (years, median [Q1, Q3])	5 (2, 9)	NA	5 (2, 9)
BMI adults (kg/m^2, mean ± SD)	25.9 ± 4.5	25.3 ± 4.0	25.5 ± 4.1
Comorbid conditions (*n* [%])	19 (59.4)	28 (82.4)	47 (71.2)
Gastrointestinal	6 (18.8)	9 (26.5)	15 (22.8)
Respiratory/thoracic	4 (12.5)	9 (26.5)	13 (19.7)
Neoplasms	3 (9.4)	8 (23.5)	11 (16.7)
Vascular	2 (6.3)	9 (26.5)	11 (16.7)
Reason for prescription[1] (n [%])			
Primary immunodeficiency	16 (50.0)	17 (50.0)	33 (50.0)
Secondary immunodeficiency	11 (33.4)	12 (35.3)	23 (34.8)
Immunomodulation	8 (25.0)	3 (8.8)	11 (16.7)
IVIG infusions per patient			
Dose (mg/kg, mean ± SD)	492 ± 347	296 ± 157	391 ± 282
No. of infusions (median [Q1, Q3])	3.5 (1, 5)	4.0 (2, 6)	4.0 (2, 6)
Previous exposure to IVIG (n [%]) Naïve	15 (46.9)	13 (38.2)	28 (42.4)
To Flebogamma DIF only	7 (21.9)	10 (29.5)	17 (25.8)
To Flebogamma DIF and other IVIG	7 (21.9)	6 (17.6)	13 (19.7)
To IVIG other than Flebogamma DIF	3 (9.3)	5 (14.7)	8 (12.1)

BMI, body mass index; IVIG, intravenous immunoglobulin; Q1, Q3, interquartile range; SD, standard deviation.
[1]There could be some patients with more than one indication.

Table 2. Patients experiencing adverse events (AEs) for each group of treatment, classified according to relatedness (AEs potentially related to study products), seriousness (serious [SAE], nonserious), and severity (severe, moderate, mild).

	Flebogamma DIF 10% (*N* = 32)		Flebogamma DIF 5% (*N* = 34)	
	Subjects (*n*, %)	AEs (*n*)	Subjects (*n*, %)	AEs (*n*)
Total patients with AEs	11 (34.4)	40	12 (35.3)	26
Relatedness				
Not related	2 (18.2)	8	9 (75.0)	13
Potentially related	9 (81.8)	33	3 (25.5)	8
Seriousness				
SAEs	4 (36.4)	10	3 (25.0)	7
Nonserious	7 (63.6)	30[1]	9 (75.0)	19
Severity[2]				
Moderate	1 (66.7)	6	1 (100)	6
Unrated	1 (33.3)	1	0	0

[1]Seventeen of them in the same patient.
[2]For SAEs potentially related to treatment.

Discussion

Data from clinical studies suggest a higher rate of AEs associated with infusions of IVIG 10% compared to less concentrated formulations. Moreover, whether frequency of serious but less common AE is higher with concentrated IVIG products remains unclear. In this surveillance study, performed under routine clinical practice conditions, we observed that no unpredictable risk or concern for patients was detected for both 10% and 5% concentrations of Flebogamma DIF, which were therefore deemed safe and well tolerated in a population stable on IVIG. The frequency of infusions associated with AEs was lower with the 5% product, although the type, seriousness, and severity of AEs reported were similar for both concentrations and consistent with the literature.

There are few studies comparing 10% versus 5% formulations, and even fewer comparing different strengths of the same product as presented herein (since both Flebogamma DIF 5% and 10% share the same fractionation and purification phases, and the concentration is then adjusted to either 5% or 10%), and the results are variable. In clinical trials performed with Flebogamma DIF (the evolution of Flebogamma), a difference of around 20% points between 10% and 5% products (10.8% and 30.5%, respectively) is observed in the rate of infusions with potentially related AEs in relation to the number of infusions (Berger 2007; Ballow 2009; Julia et al. 2009; Berger et al. 2010).

Table 3. Classification and number of adverse events (AEs) and serious AEs (SAEs) according to system organ class and preferred term affected.

Disorder and type of AE	Flebogamma DIF 10% (*n*)	Flebogamma DIF 5% (*n*)
Nervous system		
Headache	17[1]	0
General and administration site		
Pyrexia	6 (1)	0
Chest pain	1 (1)[2]	1 (1)[2]
Chills	1 (1)[2]	1 (1)[2]
General physical health deterioration	1 (1)[2]	0
Infections and infestations		
Fungal	0	1
Viral	2	2
Bacterial	2	5
Gastrointestinal		
Vomiting	1	1
Diarrhea	1	1
Abdominal pain upper	1	0
Constipation	0	1
Rectal bleeding	0	1 (1)
Respiratory, thoracic, and mediastinal		
COPD	2 (1)	0
Dyspnea	1 (1)[2]	1 (1)[2]
Bronchoaspiration pneumonia	1 (1)	0
Pulmonary edema	0	1 (1)
Immune system		
Hypersensitivity	2 (2)[2]	1 (1)[2]
IgG subclass deficiency	0	1
Cardiovascular		
Cardiac disorder	0	1
Increased blood pressure	1 (1)[2]	1 (1)[2]
Dermatological		
Actinic keratosis	0	1
Rash	0	1
Renal and urinary (renal failure)	0	2
Musculoskeletal (back pain)	0	1
Vascular (hematoma)	0	1

Numbers in parentheses indicate SAEs.
[1]Fifteen of 17 in the same patient.
[2]AEs potentially related to treatment.

In the Flebogamma DIF 5% product, 18.5% of infusions were associated with AEs and 2.2% of infusions were associated with AEs potentially related to the product. A difference of around 15–16% more infusions associated with AEs was observed in the 10% concentration (33.1 vs. 18.5% with the 5% concentration). This is consistent with what can be observed when comparing clinical trials with these products (Berger 2007; Ballow 2009; Julia et al. 2009; Berger et al. 2010). Hence, Berger et al. (2010) reported that 48.4% of Flebogamma DIF 10% infusions in PID patients (adults and children) were associated with AEs.

It should be taken into account that patients with autoimmune diseases are usually treated with high IVIG doses and, in our study, most of them (8 of 11) were included in the 10% product group. Nevertheless, of these 11 patients, 8 had ITP, in which cases the number of doses is usually relatively low (Cines and Bussel 2005). Moreover, the immunomodulatory dose of IVIG was 743 mg/kg, lower than the typical dose of 1–2 g/kg (Johnston and Hollingsworth 2016), and represented only a small portion of all infusions (13.2%). Treatment-related AEs were not particularly associated with immunomodulatory doses (Fig. 2). Also, it is important to consider that all children were included in the 10% product group, of which 46.2% experienced treatment-related AEs compared with 15.8% of adults in the same 10% group. Regrettably, when it came to the interpretation of the impact of age on infusion-related AEs in the 10% treatment group, it was difficult since the published studies reporting safety of 10% IVIG products in adults and children (whether in PID/SID [Church et al. 2006; Gelfand and Hanna 2006; Stein et al. 2009; Sleasman et al. 2010; Wasserman et al. 2012; Blazek et al. 2015; Krivan et al. 2015] or in autoimmune disease [Robak et al. 2009; Blazek et al. 2015]) do not assess their results according to patient's age. Clinical study population analyses reported in the literature have shown that children and elderly may be more susceptible to AEs of treatments in general (Woods et al. 2005; Priyadharsini et al. 2011; Alomar 2014). Nevertheless, in our study, none of the SAEs potentially related to the tested product was associated with children or with patients treated with immunomodulation IVIG dose. Importantly, with the adequate infusion protocol, IVIG 10% can be safely administered to children (Lozano-Blasco et al. 2014; Kaba et al. 2017), which is in accordance with our observations.

Globally, data of safety and tolerability of 10% IVIG products reported in recent clinical trials performed in PID/SID patients (Bjorkander et al. 2006; Gelfand and Hanna 2006; Kallenberg 2007; Stein et al. 2009; Sleasman et al. 2010; Blazek et al. 2015; Krivan et al. 2015) or ITP (Bussel et al. 2004; Bussel and Hanna 2007; Robak et al. 2009, 2010) are highly variable. The rate of infusions with potentially related AEs relative to the total number of infusions range from 4.1% (Gelfand and Hanna 2006) to 71.7% (Krivan et al. 2015), and the rate of patients experiencing at least 1 AE relative to the total number of patients range from 20.0% (Kallenberg 2007) to 87.1% (Robak et al. 2010). Our results of 33.1% and 34.4%, respectively, fall well within these ranges. The observed types, seriousness, and severity of all AEs and those

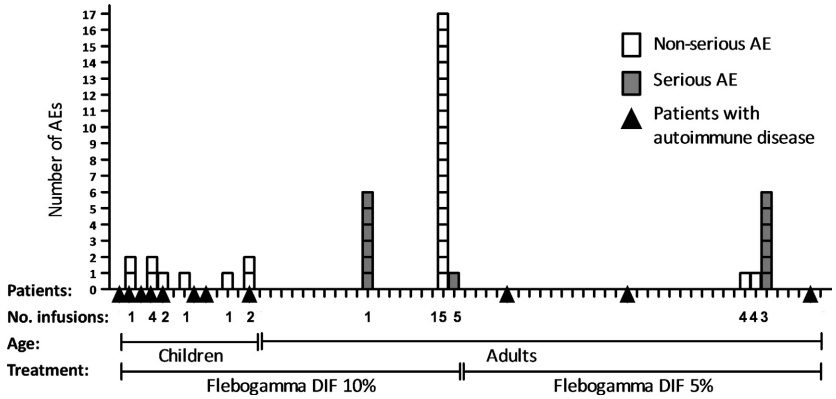

Figure 2. Number of adverse events (AEs) and serious AEs (SAEs) potentially related to treatment observed in the patients, individually represented in the abscissa axis and grouped according to treatment (10% or 5% intravenous immunoglobulin product) and age (decreasing order from left to right). Each square represents a single AE experienced by a patient (blank: nonserious; gray: SAE), which may stack as numbered in the ordinate axis. The two patients experiencing six SAEs each were associated with single allergic reactions in two respective infusions.

potentially related to Flebogamma DIF observed in this study and other clinical trials do not suggest an increased risk for any AEs other than those typically expected with IVIG products administered in different populations. The most common AEs reported in our study, independent of product concentration, are in agreement with the results published in the other studies with IVIG (Colovic et al. 2003; Pierce and Jain 2003; Roifman et al. 2003; Bussel et al. 2004; Robak et al. 2009) in which IVIG therapy was shown to be normally safe and well tolerated.

The type, seriousness, and severity of AEs registered in our study showed similar patterns between product presentations, which has previously been observed (Kuitwaard et al. 2010; Rappold et al. 2016). Globally, AEs were consistent with those presented by the patients in previous clinical trials or in normal clinical practice (Orbach et al. 2005). Accordingly, the most commonly reported symptoms were headache (all episodes occurred during the study were related to the treatment) and pyrexia, which is known to occur after IVIG treatment. Headache is the most common (>1/10) AE reported in a previous clinical study with Flebogamma DIF 10%, and fever is classified as common (>1/100 to <1/10) (Berger and Pinciaro 2004). In the current study, all episodes of headache ($n = 17$) and pyrexia ($n = 6$) were associated with the 10% product, which means that the rate of other AEs between the 10% and the 5% product was more balanced. Moreover, the fact that 15 headache episodes were observed in the same patient and four pyrexia episodes were observed in two patients indicate that unknown conditions may predispose some patients to experience AEs following IVIG infusions (Priyadharsini et al. 2011; Alomar 2014), even at slow infusion rates (infusion rate, which if fast is known to be related to the occurrence of AEs, was not always recorded in this study). Those patients who did not tolerate the 10% strength could preferentially continue receiving the 5% strength product.

Other common potentially treatment-related AEs in clinical studies with Flebogamma DIF 10% are tachycardia, hypotension, nausea, back pain and myalgia, pain and rigors, and pyrexia (Berger et al. 2010; Ballow 2013), which are among the most reported postauthorization AEs. None of them were observed in this study. With the exception of dyspnea, all the other symptoms experienced by the patients in this study are described in the product SPC as AEs related to treatment occurring uncommonly, according to observations from clinical studies (SPC, 2009). In addition, there were three hypersensitivity reactions reported, which are also well described in patients treated with blood-derived proteins (Orbach et al. 2005; Roifman et al. 2008). All patients who experienced AEs recovered after stopping the infusion or after receiving standard treatment.

Being a noninterventional and observational study constitutes the main limitation of this study. Therefore, confounding factors such as the population selection bias may be present, for example, patients who have tolerated IVIG infusions prior to the study. However, it should be highlighted that more than 55% of the patients were naïve or previously treated with IVIG other than Flebogamma DIF, which considerably reduces the chances of such bias. In addition, some details of the clinical records of the patients might not have been previously collected in the medical history leading to a possible issue of misclassification. The overall population analyzed (66 patients and 265 infusions) was greater than the originally planned sample size (225 infusions) to reach significance in the study. In addition, the design of this study does not allow

a generalization of the results beyond the approved indications or in other clinical practice setting.

In summary, no unpredictable risk was detected in either formulation of Flebogamma DIF in pediatric and adult patients receiving this product for approved indications. The frequency of infusions associated with AEs was lower in Flebogamma DIF 5%, confirming the already described frequency in previous clinical trials. Nevertheless, the nature, seriousness, and severity of AEs that occurred with both formulations showed similar patterns. These results allow the conclusion that, in the global framework of IVIG therapy, administration of both Flebogamma DIF 10% and Flebogamma DIF 5% were safe and well tolerated.

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Disclosures

MM and XO are employees of Grifols. LA, AM, EM, JPo, ED, JPa, GG, RC, and MG declare no other conflict of interest related to this paper.

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