Thrombosis Research 133 (2014) 1045–1051

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Symptomatic thromboembolic events in patients treated with intravenous-immunoglobulins: Results from a retrospective cohort study

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ARTICLE INFO

Article history:
Received 22 January 2014
Received in revised form 24 March 2014
Accepted 27 March 2014
Available online 1 April 2014

Keywords:
Thromboembolism
Immunoglobulin therapy
Pharmacoepidemiology
Incidence studies
Comorbidity

ABSTRACT

Aims: To estimate the incidence and predictors of symptomatic arterial and venous thromboembolic events (TEE) from intravenous immunoglobulin (IVIg) therapy according to its indications.
Methods: We performed a retrospective cohort study of patients seen at our institution and treated with IVIg over a 36-month period. Indications, comorbility and comedication associated with TEE were identified by a stepwise logistic regression analysis.
Results: Of 303 patients included with at least one infusion of IVIg over three years, TEE were identified in a total of 50 patients treated with IVIg, for an incidence of 16.9% (CI 95%: 13.0–21.6); 27 (54%) arterial (9.1%;CI 95%: 6.3–13.0%) and 23 (46%) venous TEE (7.8%; CI95%: 5.2–11.4%), overall mortality was 32%. Per indication there were more patients with autoimmune conditions, secondary immunodeficiency, dysimmune neuropathies, acute rejection of solid organ transplantation and sepsis. Patients with TEE were significantly older, were more likely to be men, they had more comorbid conditions; the doses of IVIg were high (589.4 mg/kg/day vs 387.0 mg/kg/day, $p < 0.001$) and differences in comedication were found. The stepwise logistic regression analysis retained high doses of IVIg (OR 3.03; CI 95%: 1.49–5.67) and diuretics therapy (OR 1.69; CI 95%: 1.06–3.97) when combined with the usual comorbid confounders.
Conclusions: The incidence of TEE from IVIg therapy remains high at one in six patients treated. The most remediable factor is a high daily IVIg load. Decreasing the daily IVIg dose together with carefully weighing diuretics therapy and comorbid risk factors may be the keys to saving lives.

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Introduction

The reported incidence of adverse events from intravenous immunoglobulin (IVIg) therapy varies widely, from 1% to 81% of patients; [1] most studies report adverse events between 30% and 40% of the infusions [2]. Immediate adverse reactions following IVIg administration are usually mild and transient flu-like symptoms, changes in blood pressure and tachycardia [3,4]. These reactions improve or wane following a reduction in the flow rate of IVIg infusion and pretreatment with analgesic, nonsteroidal anti-inflammatory drugs, antihistamines or intravenous glucocorticoids [5]. Severe anaphylactic/anaphylactoid reactions following IVIg administration are rare [6]. The role of anti-IgA antibodies in causing anaphylaxis in IgA-deficient patients receiving IVIg therapy is still controversial [7]. Late adverse events may be severe: acute renal failure, aseptic meningitis, neutropenia, autoimmune hemolytic anemia, skin reactions, arthritis and pseudohyponatremia. Probably the most important of the late events are thromboembolic events (TEE) including myocardial infarction, cerebrovascular accidents, deep vein thrombosis, pulmonary emboli, central retinal vein occlusion and hepatic veno-occlusive disease [8–12]. In 2002 the FDA required updated package labeling to include a warning about the risk of thrombotic events [13]. In limited retrospective series, the incidence of thrombotic events varies from 3% [14] to 11.2%. [15] Some authors have described a higher risk with increasing age, hypertension and dyslipidemia [8] or vascular risk factors [16]. However, no study has attempted to determine the frequency and predictors of TEE with IVIg according to the indication and taking into account comedication. As a result of the persistent uncertainties, appropriate clinical risk-assessment and consideration of alternative treatments are currently inadequate.

We studied a retrospective cohort of patients who received IVIg over a 3-year period. Our objective was to estimate the incidence of IVIg-

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http://dx.doi.org/10.1016/j.thromres.2014.03.046
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related TEE in our patients, as well as to attempt to establish the predictors and differential characteristics between venous and arterial events.

Methodology

Study Design

This was an observational, retrospective cohort study of patients treated with IVIg. We identified patients who had a TEE within 30 days of IVIg treatment completion. The needed sampling was determined to be 280 patients (margin of error ± 10%, 95% CI). The sample size for logistic regression showed that accepting alpha risk of 0.05 and a beta risk of 0.2, for a proportion of events between 10% and 16%, between 192 and 271 subjects were needed to recognize as statistically significant odd ratio greater than or equal to 1.7 [17]. Information was collected according to protocol. A case report form was completed with these details. Approval was obtained from the Institutional Review Board at La Paz University Hospital, protocol PI-1090.

Setting and Participants

This study was conducted at La Paz University Hospital in Madrid, Spain, a tertiary-care teaching hospital with 1,365 care beds. It serves a population of 787,000, plus 550,000 additional children (reference population) and 1,089,472 additional women (gynecology and obstetrics). In addition, it is a national referral hospital for certain clinical situations (Immunodeficiency syndromes, critically burned patients, solid and alogenic organ transplantation, pediatric ophthalmology, pediatric hemato-oncology), but we cannot attribute a precise reference population for those conditions. We identified patients who had a prescription for IVIg between January 1, 2008, and December 31, 2010.

Study Outcomes

We examined the following diagnoses and codes for venous thromboembolic disease: deep vein thrombosis (ICD-9-CM codes: 453.40 to 453.42) pulmonary embolism (415.19, 415.11 and 415.12), acute myocardial infarction (410.10 to 410.92), mesenteric thrombosis and embolism (557.0), arterial embolism and thrombosis (444.0 to 444.9), embolism and thrombosis portal (452), embolism and thrombosis of intracranial venous sinus (325), venous complications in pregnancy and puerperium (325), embolism or venous thrombosis in unspecified vein (453.9), other stroke and venous thrombosis (634.6, 635.6, 636.6, 637.6, 638.6 and 639.6), puerperal pulmonary embolism (673.2), thrombus (thromboembolism) following infusion, perfusion or transfusion (999.2), occlusion of central retinal vein (362.35) branch retinal vein (362.36). Diagnoses and codes of arterial thromboembolic disease: acute stroke (ICD-9-CM codes: 434.9X to 434.0X), transient ischemic attack (435.9), acute coronary syndrome (411.0 to 411.89), acute arterial ischemia (435.0 to 435.9), acute myocardial infarction (410.10 to 410.92), cardiogenic shock (785.51, as secondary diagnosis) and cardiorespiratory arrest (427.5). We included data for all study outcomes through January 31, 2011. The length of follow-up in all analyses was until discharge, transfer or decease after the index date.

Data Sources

We obtained IVIg prescriptions from the database of the hospital pharmacy department between January 1, 2008 and December 31, 2010. Clinical records were used to confirm the administration of IVIg and the clinical indication, the presence of TEE, its type, timing of confirmatory diagnostic tests performed and the outcome. Patients out of the reference population at the time of TEE were excluded from the cohort of IVIg. A review of records also noted the presence of the following risk factors for TEE: gender, age, comorbidity and comedication. The time of TEE in relation to the IVIg course of treatment was ascertained. The most frequent comedication of patients with TEE was compared with patients without TEE at the moment of onset. Drugs were categorized by Therapeutic Subgroups using the Anatomical Therapeutics Chemical (ATC) classification system.

Statistical Analysis

We describe the characteristics of the treatment groups on the index date by presenting the frequency distribution for categorical variables and the medians and ranges for continuous variables. The incidence rate of TEE in patients treated with IVIg was calculated by dividing the number of TEE by the number of patients treated with an IVIg during the period of the study. Uncertainty of estimation was assessed by calculation of the two-sided Wald 95% confidence interval. The χ^2-test or Fisher's exact test was performed for all categorical variables, and Student's t-test and the Mann Whitney test were employed, as appropriate, for continuous variables. Variables associated with a TEE at $p \leq 0.10$ in the univariate analysis were entered into a stepwise logistic regression model to obtain estimates effects; the rate of events per variable was at least 10. The age of adult patients and the dose of IVIg were dichotomized at the media for the analysis. We used commercially available software (SPSS, version 17, IL, US) for all statistical analyses.

Results

General Background

We identified 591 patients with at least one infusion of IVIg over three years. They were 49.8% females. The mean age of the patients was 41 years (SD, 27; range 0 to 94 years). Of them, 303 patients received their community-based health care from this hospital. Of those, TEE were identified in a total of 56 patients treated with IVIg; 6 patients were excluded because the TEE was before IVIg treatment and 50 patients had a TEE after IVIg therapy, representing an incidence of 16.9% (CI95%:13.0 to 21.6); 27 (54%) arterial TEE (9.1%;CI95%:6.3 – 13.0%) and 23 (46%) venous TEE (7.8%;CI95%:5.2 – 11.4%), overall mortality was 32% of cases.

Case Reports

Out of 50 affected patients, the mean age of affected patients was 60.6 years (SD 28.2), 66% males. The outcome of the TEE was fatal in 16 (32%) patients. TEE occurred with 3 different IVIg brands, all except one, at 5% concentrations. Arterial thromboembolic events included acute myocardial infarction (8 cases), acute stroke (5 cases), cardiorespiratory arrest (5 cases), cardiogenic shock (4 cases), acute arterial ischemia (3 cases), and transient ischemic attack (2 cases). Venous thrombosis events included deep vein thrombosis (11 cases), pulmonary embolism (7 cases), IVC thrombosis (3 cases), mesenteric thrombosis and embolism (2 cases). A summary of the demographic characteristics and indications for IVIg treatment for patients without TEE compared to those with TEE are shown in Table 1. Patients with TEE were significantly older, more were men, and the doses of IVIg were higher (589.4 mg/kg/day vs 387.0 mg/kg/day, $p < 0.001$). Per indication there were more patients with autoimmune conditions, secondary immunodeficiency, dysimmune neuropathies, acute rejection of solid organ transplantation and sepsis (Table 1). Significant risk factors for TEE included atrial fibrillation, coronary disease, diabetes, dyslipemia, hypertension, immobility neoplasia, recent surgery, solid organ transplantation and having four or more risk factors (Table 2). Comedication with diuretics, immunosuppressants, monoclonal antibodies and prepared hematinics was significant more frequent in TEE patients; treatment with antithrombotic and platelet aggregation inhibitors was less frequent in TEE patients (Table 2). Arterial TEE were documented in clinical records after a median of 1 day (0-20 days) after the

Table 1
Summary of demographic characteristics and indications for IVIg treatment in patients without TEE vs. in patients with TEE occurring within 30 days of IVIg treatment completion.

	Patients without TEE (N = 246)	Patients with TEE (N = 50)	Significance (p)
All			
Age (years)			
Median (range)	53 (0 -99)	63.5 (0.25-89)	0.042
Mean (SD)	49 (25)	60.6 (28.2)	
Sex (% of female)	54.9	34	<0.001
Adults, n(%)	209 (85)	42 (84)	
Age (years)			
Median (range)	60 (19-99)	66 (20-90)	0.017
Mean (SD)	57 (18.9)	67 (17.9)	
Sex (% of female)	55.0	35.0	<0.001
Children(*), n(%)	37 (15)	8 (16)	
Age (years)			
Median (range)	4 (0.24-17)	7.5 (0-16)	0.098
Mean (SD)	6 (6.1)	8 (5.3)	
Sex (% of female)	54.05	25.0	<0.001
IVIg dose (mg/kg/day), mean (SD)	387.0 (316.4)	589.4 (380.8)	<0.001
Number of infusions	5 (1-37)	4 (1-18)	0.671
Indication			
Acute rejection of Solid Organ Transplantation	13 (5.3)	6 (12.0)	0.044
Atopic dermatitis	4 (1.6)	0 (0)	0.813
Autoimmune myelitis	1 (0.4)	1 (2.0)	0.759
Autoimmune uveitis	2 (0.8)	0 (0)	1.000
Chronic immune thrombocytopenia purpura	22 (8.9)	0 (0)	0.057
Connective-tissue disorder	5 (2.0)	5 (10.0)	0.016
Dermatomyositis, Polymyositis	6 (2.4)	0 (0)	0.572
Guillain Barre	2 (0.8)	1 (2.0)	1.000
Hemolytic anemia	4 (1.6)	2 (4.0)	0.592
Immune mediated thrombocytopenia	47 (19.1)	2 (4.0)	0.009
Immune neutropenia	4 (1.6)	0 (0)	0.813
Infection in immunocompromised patient	12 (4.9)	5 (10.0)	0.156
Isoinmunization	3 (1.2)	1 (2.0)	1.000
Kawasaki Syndrome	7 (2.8)	0 (0)	0.486
Lambert-Eaton syndrome	2 (0.8)	0 (0)	1.000
Multifocal motor Neuropathy	6 (2.4)	1 (2.0)	1.000
Multiple Sclerosis	5 (2.0)	0 (0)	0.678
Myasthenia gravis	6 (2.4)	2 (4.0)	0.887
Pediatric VIH-1	2 (0.8)	0 (0)	1.000
Primary immunodeficiency syndromes	52 (21.1)	1 (2.0)	0.003
Secondary immunodeficiency	23 (9.3)	12 (24.0)	0.003
Sepsis	6 (2.4)	5 (10.0)	0.030
Toxic epidermal necrolysis	4 (1.6)	0 (0)	0.813
Vasculitic polyarteritis nodosa	5 (2.0)	1 (2.0)	1.000
Wegener disease	3 (1.2)	5 (10.0)	0.003

(*) Children under 18 years of age; TEE, thromboembolic events. P value is the value of Chi-squared test for sex distribution and for the clinical characteristics or the value of Student's t or the Mann Whitney test, as appropriate.

end of the treatment ($p = 0.009$). The median to occurrence of a venous TEE was 10 days (range 0 to 27 days) after IVIg treatment (Table 3). A comparison of patients with arterial events vs. patients with venous events is shown in Table 3. The stepwise logistic regression retained high dose of IVIg (OR 3.03;CI95%:1.49 – 5.67) and diuretics therapy (OR 1.69;CI95%:1.06 – 3.97) when combined with the usual clinical confounders (Table 4).

Discussion

Various mechanisms of thrombosis following IVIg infusion have been described in the literature, and the most common is a dose-dependent relationship that increases plasma viscosity [1,18–23]. This increase is due to a high protein load following IVIg administration (IVIg can increase serum levels of IgG over three-fold to 6000 mg/dl) [1,24]. In healthy patients this increase is often insignificant, but in patients with other risk factors such as vascular disease and those with an already elevated plasma viscosity, (e.g. polycythemia, paraproteinemia, inflammation, hypercholesterolemia, leukocytosis, or dehydration thromboembolic events may be precipitated by this phenomenon) [18]. In addition, blood viscosity is one determinant of oxygen delivery to the tissues, and viscosity changes can lead to a decrease in cardiac perfusion [25]. A relationship between IVIg administration and cerebral vasospasm has also been suggested by Sztajzel et al. [26].

During the second and third quarters of 2010 there was an increase in thromboembolic event reports in several European countries resulting in the withdrawal of all batches of one brand of commercial IVIg [27]. It is possible that the presence of clotting factors and blood products is due to inadequate purification processes of the manufacturer [28]. Out of 50 TEE during the study period (three years), only 6 cases were recorded during second or third quarters of 2010, probably due to low use of the affected batch in our hospital.

Association with Indications for IVIg Treatment

TEE appear with varying frequencies according to indications. TEE are usually associated with neurologic and autoimmune diseases. The thrombosis incidence varies between 1.1% and 4.5% in neurological patients and up to 13% in autoimmune patients, [8,15,29,30] 10.2% and 16.9% respectively in our study. Patients with primary immunodeficiency syndromes less frequently develop TEE. Primary immunodeficiency syndromes or immune mediated thrombocytopenia are less prone to develop thrombotic complications [31,32] compared to secondary immunodeficiencies [33,34], such as the hypercoagulability state during transplantation [35], the high number of comorbid conditions in solid transplant recipients [36] or the activation of coagulation that frequently occurs in severe infections or sepsis [37].

Table 2
Individual risk factors of IVIg treatment for patients without TEE vs. for patients with TEE occurring within 30 days of IVIg treatment completion.

	Patients without TEE (N = 246)	%	Patients with TEE (N = 50)	%	significance
Individual risk factors					
Antiphospholipid antibodies	0	0.0	1	2.0	0.376
Antithrombin deficiency	0	0.0	1	2.0	0.376
Atrial fibrillation	4	1.6	5	10.0	0.007
Burn	6	2.4	1	2.0	1.000
Coronary disease	9	3.7	14	28.0	<0.001
Diabetes	34	13.8	20	40.0	<0.001
DVT or Pulmonary embolism (history of)	3	1.2	2	4.0	0.430
Dyslipidemia	33	13.4	18	36.0	<0.001
Fetal anemia by maternal isoimmunization anti-kell	0	0.0	1	2.0	0.376
Hemodialysis	19	7.7	4	8.0	1.000
Hyperhomocisteine	1	0.4	1	2.0	0.759
Hypertension	56	22.8	22	44.0	0.002
Immobility	17	6.9	15	30.0	<0.001
Lupus anticoagulant	2	0.8	1	2.0	1.000
Myeloproliferative disease	2	0.8	1	2.0	1.000
Neoplasia (*)	34	13.8	15	30.0	0.005
Nephrotic syndrome	27	11.0	2	4.0	0.211
Obesity	21	8.5	3	6.0	0.753
Recent surgery	16	6.5	12	24.0	<0.001
Recent trauma	11	4.5	2	4.0	1.000
Resistance or protein C or S deficiency	1	0.4	1	2.0	0.759
Shock	20	8.1	3	6.0	0.823
Solid Organ Transplantation	13	5.3	9	18.0	0.002
Stroke or transient ischemic attack(history of)	6	2.4	2	4.0	0.887
≥ than 4 risk factors	48	19.5	34	84.0	<0.001
Comedication (**)					
Analgesics	7	2.8	1	2.0	1.000
Anestesics	8	3.3	2	4.0	1.000
Antiepileptics	6	2.4	2	4.0	0.887
Antihypertensive	54	22.0	12	24.0	0.896
Anti-inflammatory and antirheumatic products	32	13.0	6	12.0	1.000
Antineoplasic agents	12	4.9	6	12.0	0.110
Monoclonal antibodies	4	1.6	5	10.0	0.007
Others	8	3.3	1	2.0	0.985
Antithrombotic agents (#)	106	43.1	14	28	0.048
Blood substitutes and perfusion solutions	15	6.1	5	10.0	0.488
Cardiac stimulants excl cardiac glycosides	8	3.3	1	2.0	0.985
Diuretics	36	14.6	18	36.0	<0.001
Drugs for bone diseases	12	4.9	5	10.0	0.156
Endocrin therapy	7	2.8	2	4.0	1.000
Immunossuppresants	11	4.5	6	12.0	0.037
Immunostimulants	9	3.7	4	8.0	0.324
Parenteral nutrition	13	5.3	5	10.0	0.343
Platelet aggregation inhibitors	105	42.7	12	24	0.045
Prepared haematinics	9	3.7	8	16.0	0.001
Psychoanaleptics	9	3.7	2	4.0	0.878
Psycholeptics	5	2.0	2	4.0	0.746

(*) Only malignancies were recorded, myeloproliferative diseases were considered separately.
(**) Therapeutic subgroup of ATC classification.
(#) excepting platelet aggregation inhibitors; DVT, Deep venous Thrombosis; excl, excluded; P value is the value of the Chi-squared test.

Association with the Daily Dose of IVIg

Although patients have developed thrombosis while receiving IVIg at the recommended rate and dose, we noticed that a significant number of patients who experience thrombotic events have received daily doses and infusion rates higher than what is recommended (387.0 vs. 589.4 mg/kg/day, $p < 0.001$), data in concordance with other authors [1,18]. Therefore, several authors have proposed that daily doses should be administered over at least 8 hours to minimize the risk, and those at high risk of developing thrombosis should receive a maximum daily dose of 400 mg/kg [1,18,38]. It is important to note that infusion rates based on patient tolerance of the drug should be avoided, as TEE can occur after numerous previously uncomplicated treatment cycles, [1,30,39] up to 18 infusions in this study.

Associated Individual Risk Factors

Standard thrombosis risk factors such as hypertension, diabetes mellitus, and ischemic heart disease are relevant to IVIg recipients [1]. We also found that atrial fibrillation and burns are risk factors for arterial events, probably due to the activation of platelets and the coagulation system. The risk of developing a venous thrombotic complication following IVIg is increased in patients who are elderly, who have renal impairment, pre-existing vascular disease, monoclonal gammapathy, hyperlipidemia and immobilization [1,10,24,30,40].

Time to Onset

The serum half-life of IgG is 23 days, which is much longer than for IgM (5 days) and IgA (7 days). The long serum half-life of IgG is attributed to the neonatal Fc receptor, known as FcRn, which is composed of MHC class I-related protein and B2-microglobin. IVIg preparations have a similar blood half-life as endogenous immunoglobulin, thus monthly replacement therapy is usually adequate. We found that the time to onset arterial events was 1 (0-20) day and venous events 10 (0-27) days. However, the half-life of IgG can be abnormally short (<10 days) in certain conditions, e.g. protein-losing enteropathy, nephrotic syndrome, IgG paraproteinemia, and myotonic dystrophy. Thus, one of

Table 3
Characteristics of patients with venous vs. arterial events.

	Patients with arterial events N, (%)	Patients with venous events N, (%)	significance
All	27 (54)	23 (46)	0.108
Age (years)			
Median (range)	59 (3-89)	66 (0.3–86)	0.743
Mean (SD)	51.5 (27.7)	60 (23)	
Sex, n (% of female)	10 (24.49)	8 (34.8)	0.030
Adults, n (%)	24 (88.9)	19 (82.6)	0.096
Age (years)			
Median (range)	65 (37-89)	67 (19-86)	0.916
Mean (SD)	67.4 (11.4)	65 (15.3)	
Sex, n (% of female)	8 (33.3)	8 (42.1)	0.074
Children(*), n(%)	4 (14.8)	4 (17.4)	0.493
Age (years)			
Median (range)	10 (3-15)	1 (0.25 – 10)	0.486
Mean (SD)	9.3 (4.9)	1 (0.00)	
Sex, n (% of female)	2 (50)	0 (0)	<0.001
Indication			
Acute rejection of Solid Organ Transplantation	1 (3.7)	5 (21.7)	0.129
Autoimmune conditions	9 (33.39)	6 (26.1)	0.577
Dysimmune neuropathies	4 (14.8)	1 (4.3)	0.449
Immunocompromized patient	2 (7.4)	3 (13.0)	0.850
Isoinmunization	0 (0)	1 (4.3)	0.935
Primary immunodeficiency syndromes	1 (3.7)	0 (0)	1.000
Secondary immunodeficiency	7 (25.9)	5 (21.7)	0.989
Sepsis	3 (11.1)	2 (8.7)	1.000
Individual rick-factors			
Atrial fibrillation	4 (14.8)	1 (4.3)	<0.001
Burn	1 (3.7)	0 (0)	0.049
Diabetes mellitus	14 (51.9)	6 (26.1)	<0.001
DVT or Pulmonary embolism (history of)	0	2 (8.7)	0.002
Dyslipidemia	12 (44.4)	6 (26.1)	<0.001
Hypertension	16 (59.3)	6 (26.1)	<0.001
Immobility	9 (33.3)	6 (26.1)	0.127
Ischemic heart disease	5 (18.5)	0 (0)	<0.001
Neoplasia (**)	3 (11.1)	15 (65.2)	<0.001
Obesity	2 (7.4)	1 (4.3)	0.127
Pre-existing vascular disease	0 (0)	2 (8.7)	0.002
Pro-coagulant diseases	1 (3.7)	3 (13.0)	0.006
Renal impartment	0 (0)	6 (26.1)	<0.001
Shock	1 (3.7)	2 (8.7)	0.076
Solid Organ Transplantation	4 (14.8)	5 (21.7)	0.094
Stroke or transient ischemic attack (history of)	1 (3.7)	1 (4.3)	0.767
≥ than 4 risk factors	24 (88.9)	18 (78.3)	0.010
IVIg dose (mg/kg/day)	498.4 (297.9)	644.2 (452.4)	0.049
Time to onset (days)			
Median (range)	1 (0-20)	10 (0-27)	0.009
Mean (SD)	4 (5)	11.4 (9)	
Comedication (#)			
Analgesics	1 (3.7)	0 (0)	0.049
Anestesics	1 (3.7)	1 (4.3)	0.767
Antiepileptics	1 (3.7)	1 (4.3)	0.767
Antihypertensive	5 (18.5)	7 (30.4)	0.009
Anti-inflammatory and antirheumatic products	4 (14.8)	2 (8.7)	0.030
Antineoplasic agents	4 (14.8)	2 (8.7)	0.030
Monoclonal antibodies	4 (14.8)	1 (4.3)	<0.001
Others	0 (0)	1 (4.3)	0.034
Antithrombotic agents (&)	10 (37)	4 (17)	0.049
Blood substitutes and perfusion solutions	3 (11.1)	2 (8.7)	0.394
Cardiac stimulants excl cardiac glycosides	1 (3.7)	0 (0)	0.049
Diuretics	9 (33.3)	9 (39.1)	0.234
Drugs for bone diseases	5 (18.5)	0 (0.)	<0.001
Endocrin therapy	1 (3.7)	1 (4.3)	0.767
Immunossuppresants	3 (11.1)	3 (13.0)	0.572
Immunostimulants	2 (7.4)	2 (8.7)	0.645
Parenteral nutrition	3 (11.1)	2 (8.7)	0.395
Platelet aggregation inhibitors	3 (11.1)	9 (39.13)	0.021
Prepared haematinics	6 (22.2)	2 (8.7)	<0.001
Psychoanaleptics	0 (0)	2 (8.7)	0.002
Psycholeptics	0 (0)	2 (8.7)	0.002

(*) Children under 18 years of age.
(**) Only malignancies were recorded, myeloproliferative diseases were considered separately.
(#) Therapeutic subgroup of ATC classification.
(&) excepting platelet aggregation inhibitors; DVT, Deep venous Thrombosis; excl, excluded; P value is the value of the Chi-squared test or the value of Student's t or Mann Whitney test, as appropriate.

Table 4
Variables retained in the stepwise logistic regression model to obtain estimates effects.

VARIABLE	OR	95% CI	P value
≥4 comorbid conditions	4.70	2.67 – 7.83	<0.0001
High Dose of IVIg (*)	3.03	1.49 – 5.67	<0.0001
Diuretics	1.69	1.06 – 3.97	<0.05

Significance of the statistic analysis (P).
(*) The daily dose (mg/kg) of IVIg was dichotomized at the media for the analysis.

the proposed mechanisms for the benefit of high-dose IVIg to autoimmunity is the accelerated catabolism of autoantibodies. Paran et al. [11] reviewed the time of onset in 60 case reports of thrombosis following IVIG administration; nearly half (41%) of the events occurred within 4 h of IVIG infusion. Recognizing an adverse event immediately after the infusion of an IVIg is easier than associating events 27 days after infusion, which could lead to an underestimation of the real incidence of TEE.

Association with Comedication

Comedication is a risk factor that should always be considered together with additional genetic predisposition or comorbidity. Vascular endothelial growth factor (VEGF) antagonists block VEGF from binding to its related receptor, which may lead to endothelial cell (EC) apoptosis. Most reports involve bevacizumab, an anti-VEFG monoclonal antibody [41]. Diuretics induced systemic dehydration, as shown by a decrease in total body mass through changes in transmembrane fluid and electrolyte fluxes increasing whole blood viscosity [42]. Patients with paroxysmal atrial fibrillation and thromboembolism events have depressed left ventricular function and elevated hematocrit, probably due to high prevalence of diuretic therapy [43]. The immunosuppressive agent cyclosporine has a thrombotic effect through changes in the metabolism of ECs. These changes lead to cell detachment and increases in platelet activation [44]. Glucocorticoids increased the level of thrombotic factors and decreased fibrinolytic activity, [45] as did hormone replacement therapy [46]. Prepared hematinics have a thrombotic effect due to increased vascular resistance by changing the balance between vasodilatory and vasoconstrictive prostaglandins. In addition, increased red blood cells mass lead to an augment in blood viscosity [47]. Cardiac stimulants and psychoanaleptics cause vasoconstriction [48,49] and psycholeptics increase serotonin and prolactin levels, inducing platelet activation. This causes an elevation in antiphospholipid antibodies level and may also induce arterial hypotony and peripheral vasodilation, leading to blood stasis [50].

The protective effects of antithrombotic agents (excluding the paradoxical effect of heparin-induced thrombosis via an auto-immune response to platelet-heparin complex), and platelet aggregation inhibitors was not retained in the logistic model probably because of linearity with the other variables, however we think that they could help prevent the high incidence of thromboembolic events during IVIg therapy (Table 2).

Advantages and Limitations of the Study

The study has some limitations. First, it is a retrospective study, based on chart review, although all cases of TEE were properly diagnosed with confirmatory test. Second, it is a single-centre study, thus the validity of the results need to be confirmed in other hospitals. The study was strengthened by the inclusion of almost all patients on IVIg treatment from 2008 to 2010.

In conclusion, thromboembolic events are the most serious complication of IVIg therapy. Their incidence remains high: as many as one in six patients treated, the overall mortality is 32% of cases. The most remediable risk factor is the high daily IVIg load. Decreasing the daily IVIg dose together with carefully weighing diuretics therapy and comorbid risk factors may be the keys to saving lives.

Funding Disclosure

The study was conducted as part of the routine work of the Pharmacy Commission of the La Paz University Hospital. However, a donation of Terumo BCT Europe of 400 € was made to help with the publication of the manuscript.

Conflict of Interest Statement

E Ramírez, JA Romero-Garrido, E López-Grandos, AM Borobia, T Pérez, N Medrano, C Rueda, HY Tong, A Herrero and Jesús Frías have no conflicts of interest that are directly relevant to the content of this manuscript.

Authors´Contributions

Program concept and design: E Ramírez and JA Romero-Garrido.

The analysis and interpretation of data were performed independently by E Ramírez, AM Borobia, N Medrano, HY Tong and reviewed by JA Romero-Garrido, T Pérez, C Rueda.

Critical writing: E Ramírez, JA Romero-Garrido and E López-Granados.

Critical revision of the manuscript for important intellectual content: J Frías, A Herrero and E López-Granados.

Final approval of the version to be published: E Ramírez, JA Romero-Garrido, E López-Granados, AM Borobia, T Pérez, N Medrano, C Rueda, HY Tong, A Herrero, J Frías.

Acknowledgements

The authors would like to thank the following study investigators: Dr. L. Krauel-Bidwell, C. Zegarra.

We are grateful to ServingMed.com for the corrections to the English grammar and academic style of the manuscript.

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