

Original Article

Efficacy and safety of ClairYg[®], a ready-to-use intravenous immunoglobulin, in adult patients with primary immune thrombocytopenia

Borhane Slama¹, Olivier Fain², Hervé Maisonneuve³, Eric Jourdan⁴, Jean-François Viallard⁵, Rabye Ouaja⁶, Ousmane Alfa-Cissé⁶, Bertrand Godeau⁷, on behalf of Study Investigators.

¹Department of Haematology, Henri Duffaut Hospital, France; ²Department of Internal Medicine, Jean Verdier Hospital, France; ³Department of Internal Medicine, Les Oudairies Hospital, France; ⁴Hematology Department, Carémeau Hospital, France; ⁵Department of Internal Medicine, Haut-Lévêque Hospital, France; ⁶Global Scientific Affairs Unit, LFB Biomedicaments, France; ⁷Department of Internal Medicine, University Hospital Henri Mondor, France

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Abstract: Purpose: The present study was designed to assess the efficacy and safety of IGNG that is a new liquid, saccharose and maltose-free highly purified ready-to-use 5% intravenous immunoglobulin (IVIg), in primary immune thrombocytopenic patients with severe thrombocytopenia. Methods: Nineteen adults with a platelet count $\leq 25 \times 10^9/L$ received a single dose of IGNG (1 g/kg) on Day 1, with a second identical dose on Day 3 if needed. Patients were followed for 30 days. Primary endpoint was the response rate, defined as the proportion of patients with a platelet count $\geq 50 \times 10^9/L$ within 96 hours after the first IGNG dose. Results: All but one of the 17 evaluable patients for efficacy responded with an overall response rate of 94.1% (95% CI 71.3%-99.9%). Response was observed after only one infusion (1 g/kg body weight) in 11 patients (59%) and the others required a second dose. Mean time to response was 2.2 days. Maximum platelet count was reached within 1 week after the first dose and lasted for approximately 2 weeks. Patients requiring a second dose had lower platelet counts at baseline than patients requiring a single dose. In the 19 evaluable patients for safety, IGNG demonstrated good safety, good hepatic and renal tolerance, and did not induce hemolysis. This trial was registered at the French Medical Agency (AFSSAPS) as #DI n° 060735.

Keywords: Intravenous immunoglobulin, primary immune thrombocytopenia, efficacy, safety

Introduction

Primary immune thrombocytopenia (ITP), also known as idiopathic or auto-immune thrombocytopenic purpura, is an acquired immune-mediated condition characterized by isolated thrombocytopenia and the absence of other causes of thrombocytopenia. Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by auto-antibodies to more complex mechanisms in which both impaired platelet production and T-cell-mediated effects play a role [1, 2].

ITP in adults has typically an insidious onset, with no preceding viral or other illness, and usually follows a chronic course [3]. Approximately 5% of patients have a chronic refractory form of ITP, defined as failure of any modality

to keep the platelet count above $20 \times 10^9/L$ for an appreciable time without unacceptable toxicity [4]. The epidemiology of ITP is not well known. The overall incidence was estimated to 3.9 per 100,000 person-years in the UK [5] and 2.9 per 100,000 person-years in France [6].

The main goal of initial treatment of acute episodes of ITP is to avoid major bleeding and to preserve patient activity. Common therapeutic modalities are systemic corticosteroids and intravenous immunoglobulin (IVIg). The ability of IVIg to increase platelet counts in the context of ITP has been supported by numerous data [1].

The common posology for IVIg therapy in adults is 0.8-1 g/kg body weight on Day 1. A second dose on Day 3 is administered in case of persistent bleeding symptoms (or on Day 2 if vital or functional prognoses are engaged). The thera-

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peutic effects of IVIg therapy are always transient and last for approximately 2 to 4 weeks. Compared to corticosteroids, IVIg has no influence on ITP natural history [1, 7].

IGNG (ClairYg[®], developed by LFB, a French plasma products company) is a ready-to-use, liquid, saccharose- and maltose-free, highly purified 5% IVIg with a high biologic safety profile. The purification process includes precipitation steps (ethanolic and caprylic) and chromatography steps (anion-exchange and affinity), resulting in a final product with all IgG functionalities preserved and low levels of IgA, IgM, and anti-A and anti-B hemagglutinins. Glycine, mannitol and polysorbate 80 are used as excipients for their stabilizing properties and/or buffering capacity. The osmolality is near the physiological range (260-320 mOsmol/kg). The pH is between 4.6 and 5.0. The manufacturing process of IGNG includes 2 dedicated viral reduction steps: a solvent-detergent treatment and nanofiltration through a 20-nm filter. Caprylic acid fractionation and anion-exchange chromatography also contribute to viral inactivation or removal. Several steps in the manufacturing process, such as caprylic acid precipitation and filter press separation, anion-exchange chromatography and nanofiltration, contribute to removal of potential transmissible spongiform encephalopathy (TSE) infectivity. No excipients of animal origin are used.

The primary aim of the present study was to assess the efficacy and safety of high-dose IGNG (up to 2 g/kg divided over 2 administrations) in patients with chronic ITP presenting with an episode of severe thrombocytopenia.

Methods

The study was a Phase II/III, multicenter, prospective, open-label, single-arm pivotal investigation of 30-day duration. The protocol was reviewed and approved by the ethics committee of CHU Pellegrin, Bordeaux, France, and registered at the French Medical Agency (AFSSAPS) as DI n°060735. The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council on Harmonisation, and local laws/regulations. Patients gave written informed consent before study entry.

The study design and objectives were chosen on the basis of the European Medicines Agency (EMA) Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for

Intravenous Administration (IVIg) [8], issued in June 2000 and current at the time of the study. All recommendations from this Note for Guidance were followed, except for the platelet count at baseline, which we increased from $\leq 20 \times 10^9/L$ to $\leq 25 \times 10^9/L$ after poor initial recruitment. This increase did not impact the target population, as platelet counts were still in the range of severe and symptomatic thrombocytopenia (≤ 20 to $30 \times 10^9/L$) for which treatment is indicated [9, 10].

Entry criteria

Male and female patients aged 18 years and older were eligible for the study if they had a diagnosis of ITP for at least 6 months and a platelet count $\leq 25 \times 10^9/L$. ITP was diagnosed in accordance with standard criteria: isolated thrombocytopenia for at least 6 months, a normal myelogram or a myelogram rich in megakaryocytes, and absence of other causes of thrombocytopenia. A myelogram was optional in patients under the age of 60 whose blood counts and blood smears were otherwise normal and in whom a response had been observed after prior treatment with corticosteroids or IVIg.

Key exclusion criteria were a history of treatment that could induce immuno-allergic purpura within 15 days prior to inclusion; documented infection with HIV or hepatitis B or C virus; systemic lupus erythematosus (≥ 4 American College of Rheumatology [ACR] criteria) [11, 12]; visceral disease or active malignant disease requiring curative treatment; severe hemorrhagic syndrome; splenectomy within a month prior to inclusion; known IgA deficiency with anti-IgA antibodies; immunoglobulin therapy within a month prior to inclusion; treatment with anti-CD20 antibody within 8 weeks prior to inclusion; initiation of corticosteroids or an increase dose within 4 weeks prior to inclusion; initiation of other ITP treatments or increase in dose within 4 weeks prior to inclusion; and chronic renal insufficiency or serum creatinine $> 120 \mu\text{mol/L}$.

Treatments

All patients received a single intravenous IGNG infusion of 1 g/kg on Day 1, with a second, identical administration on Day 3 in case of insufficient response, defined as a platelet count $< 50 \times 10^9/L$. The infusion was administered at an initial 1 mL/kg/h flow rate or below during the first 30 minutes. According to clinical

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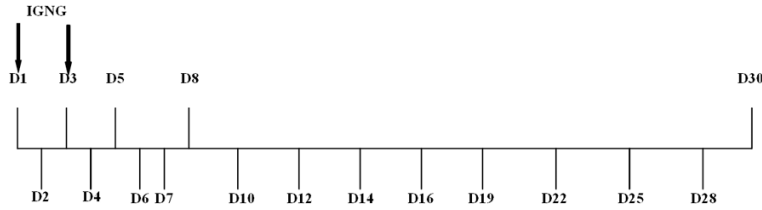


Figure 1. Study Design. Day 1 (baseline): administration of IGNG (1 g/kg). Day 3: administration of IGNG in case of insufficient response (1 g/kg). Day 5: assessment of primary endpoint. Days 1-8, 10, 12, 14, 16, 19, 22, 25, 28 and 30: assessment of platelet counts and of safety and efficacy parameters. Days 3, 5, 8 and 30: assessment of changes in clinical signs of hemorrhage (**Table 1**) and of safety and efficacy parameters.

Table 1. Graduated Clinical Scale for Assessment of Clinical Hemorrhage

Clinical Presentation	Score
Cutaneous purpura	
Localized	1
Extensive, progressive or both	3
Associated with marked ecchymosis	4
Hemorrhagic oral bullae, spontaneous gingival bleeding or both	4
Epistaxis	
Unilateral	2
Bilateral	3
Macroscopic hematuria	5
Patent gastro-intestinal hemorrhage	5
Major menorrhagia, metrorrhagia or both	4
Intra-cranial hemorrhage	15
Total score (maximum)	40

Bleeding score established by Godeau et al [13] and Khellaf et al [14].

tolerance, the infusion rate could be increased gradually to a maximum of 4 mL/kg/h.

Initiation of ITP treatments other than IGNG or changes in consisting ITP therapies were not allowed. Other disallowed therapies were corticosteroids, premedication with anti-histamines or corticosteroids, and platelet transfusion. Splenectomy was allowed if IGNG was given in preparation of the intervention and at least 96 hours before the planned date of the intervention.

Assessments

Platelet counts were determined before the first IGNG infusion on Day 1 (baseline) and at regular intervals thereafter (**Figure 1**). Platelet counts on Days 1, 3, 5, 8 and 30 were determined at the laboratories of the individual study centers, using standard methodology. Platelet counts after Day 5 were not required if relapse

was confirmed by 2 consecutive platelet counts $< 25 \times 10^9/L$.

The primary efficacy parameter was the response rate, defined as the proportion of patients with a platelet count $\geq 50 \times 10^9/L$ within 96 hours (Day 5) after the first IGNG infusion on Day 1. Secondary efficacy parameters were the time to response; the duration of response; maximum platelet count and time to reach it; relapse rate, defined as the proportion of responders with a platelet count $< 25 \times 10^9/L$ at some point during the study; time to relapse; regression of clinical hemorrhage; and need for additional ITP therapy. Clinical hemorrhage was assessed at baseline and on Days 3, 5, 8 and 30 using a graduated clinical scale [13, 14] (**Table 1**). A *post hoc* definition was adopted for partial response (at least one platelet count $\geq 30 \times 10^9/L$ between Day 2 and Day 30 with at least a doubling of the baseline count).

Safety was assessed through recording of adverse events, vital signs (temperature, blood pressure, pulse rate, respiratory rate), physical examination, and clinical laboratory parameters (hematology, hemolysis, biochemistry). Adverse events were recorded throughout the entire study. Temporally associated adverse events were defined as any adverse event, regardless of the relationship to treatment, occurring during or within 48 hours after the infusion. Vital signs were assessed before, during and after the infusion. Serum creatinine and liver function tests (transaminases, total bilirubin) were assessed before the infusion and throughout the 30-day follow-up. Signs of hemolysis were monitored before and after the infusion by measurements of hemoglobin, haptoglobin, reticulocytes, total and free bilirubin, and the direct Coombs test. If hemolytic syndrome was detected, further investigation of hemolysins and anti-A, anti-B and anti-D hemagglutinins was to be performed whenever possible.

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Table 2. Demographics and Baseline Characteristics (Safety Set, N = 19)

Sex, n (%)	
Male	6 (31.6%)
Female	13 (68.4%)
Age, years	
Mean (SD)	59.9 (19.3)
Median (range)	58.9 (18.5-98.4)
Body Mass Index, kg/m ²	
Mean (SD)	25.2 (5.1)
Median (range)	25.4 (15.8-34.6)
Diagnosis history, years	
Median (range)	3.8 (0.3-31.8)
Number of acute ITP episodes in the 12 months prior to inclusion	
Median (range)	2 (0-13)
Bleeding score	
Mean (SD)	3 (3)
Median (range)	1 (0-8)
Bleeding signs, n (%)	
Cutaneous purpura	13 (68.4%)
Localized	7 (36.8%)
Extensive, progressive or both	2 (10.5%)
Associated with marked ecchymosis	4 (21.1%)
Hemorrhagic oral bullae, spontaneous gingival bleeding or both	4 (21.1%)
Epistaxis	
Unilateral	0
Bilateral	0
Macroscopic hematuria	0
Patent gastro-intestinal hemorrhage	0
Major menorrhagia, metrorrhagia or both	1 (5.3%)
Intra-cranial hemorrhage	0

Table 3. Baseline Platelets count (Safety Set, N = 19)

Platelets count ($\times 10^9/L$)	
Mean (SD)	16 (10)
Median (range)	18 (1-41)
Platelets count ($\times 10^9/L$) by class, n (%)	
≤ 10	7 (36.8%)
10-15	0
15-20	6 (31.6%)
20-25	5 (26.3%)
> 25	1 (5.3%)

Statistical analysis

According to the aforementioned EMA Note for Guidance [8], the efficacy of IVIg products in the context of ITP should be studied in at least 15 evaluable patients. Therefore, about 20 patients were planned to be enrolled to make

sure that at least 15 patients would complete all assessments.

Data were analyzed for 2 populations: the safety set and the efficacy set. The safety set included all patients who were treated with IGNG. The efficacy set included all patients who were treated with IGNG without major protocol violation and for whom at least one platelet count was available during the 96 hours after the start of the first administration of IGNG.

The response rate with corresponding 95% confidence interval was calculated using the exact binomial method (Clopper-Pearson). A response rate of at least 60% observed

in the 96-hour period (up to Day 5) after the start of the first administration of IGNG was considered as clinically relevant. This response was expected on the basis of a published study [13] comparing IVIg and high-dose methylprednisolone (HDMP) which showed a 60% response rate with HDMP in 60 AITP patients. A sensitivity analysis was performed on the safety set. Patients who were treated but for whom no efficacy assessment was available between Day 1 and Day 5 were considered as non-responders.

As secondary efficacy parameter, relapse time was estimated using the Kaplan-Meier method. All other secondary efficacy and safety parameters were analyzed descriptively.

Statistical analyses were performed with SAS 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

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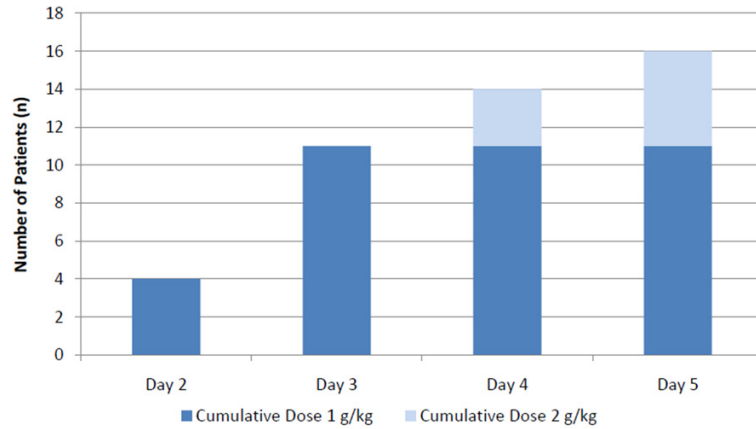


Figure 2. Number of Patients with a Platelet Count $\geq 50 \times 10^9/L$ by Day of Follow-Up and IGNG Cumulative Dose (Efficacy Set, N = 17).

Table 4. Secondary Efficacy Parameters for Platelet Response (Efficacy Set, N = 17)

Parameter	Median (range)	Mean (SD)
Time to response (days)* (n = 16)	2 days (1-4)	2.2 (1.0)
Duration of response (days)* (n = 16)	12 (3-29)	15.1 (9.3)
Maximum platelet count ($\times 10^9/L$)	160 (42-422)	172 (100)
Time to reach maximum platelet count (days)	6 (1.0-15.0)	6.4 (3.8)

*Response was defined as a platelet count $\geq 50 \times 10^9/L$ within 96 hours (Day 5) after the first IGNG infusion on Day 1.

Results

Over a one year period, 20 patients recruited from 11 centers in France were enrolled in the study. Of these 20 patients, 1 was excluded from all efficacy and safety analyses because study drug was not administered (patient with a diagnosis of ITP of less than 6 months and a baseline platelet count of $46 \times 10^9/L$). Among the 19 treated patients included in the safety set, 2 were excluded from the efficacy set due to the following major protocol violations: 1 patient received methylprednisolone in addition to IGNG on Day 1 and Day 3; 1 patient was retrospectively found not to meet the standard diagnostic criteria for ITP and in addition had a baseline platelet count of $41 \times 10^9/L$.

Patient demographics and baseline characteristics are presented in **Tables 2** and **3** for the safety set (N = 19). The majority of patients (84.2%) had been treated for previous ITP episodes, mainly with other IVIg products (73.7%) and glucocorticoids (63.2%). Six patients (31.6%) had previously undergone splenectomy. The baseline direct Coombs test was positive in 5 patients. Ten patients (52.6%)

tested positive for antibody directed against hepatitis B virus surface antigen. Thirteen patients (68.4%) presented with bleeding signs, with purpura being the most frequent (**Table 2**).

Nineteen patients received a single IGNG infusion on Day 1, and 7 required a second infusion on Day 3. The mean (\pm SD) cumulative dose was 71.7 ± 16.3 g for patients receiving a single dose and 135.7 ± 34.6 g for those requiring a second dose. These cumulative doses correspond closely to 1 and 2 g/kg, respectively. Eighteen patients received concomitant treatment for various conditions. The most frequently used therapeutic classes were anti-hypertensives, analgesics, and sedatives.

Efficacy

Sixteen of the 17 patients in the efficacy set had a platelet count $\geq 50 \times 10^9/L$ within 96 hours (Day 5) after the first IGNG infusion on Day 1 (**Figure 2**). This corresponds to a response rate of 94.1% (95% CI 71.3%-99.9%), which is significantly higher than the predefined 60% threshold for clinical relevance. Results of the sensitivity analysis in the safety set were consistent with those of the primary analysis (response 89.5%; 95% CI 66.9%-98.7%).

Eleven of the 16 responders (65%) reached a platelet count $\geq 50 \times 10^9/L$ on Day 3 and did not require a second infusion. The other 5 responders had a platelet count $< 50 \times 10^9/L$ on Day 3 and received a second infusion (**Figure 2**). The one patient in the efficacy set who did not meet the criteria of the primary efficacy parameter received 2 infusions and showed a partial response, with an increase in platelet count from $10 \times 10^9/L$ at baseline to $36 \times 10^9/L$ on Day 5.

The mean time to response was short (2.2 days) (**Table 4**). The maximum platelet count ($172 \times 10^9/L$) was generally reached within 1 week after the first IGNG infusion. It deas-

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Table 5. Baseline Platelet Count and Baseline IgG Trough Levels in Patients Treated with 1 g/kg IGNG and Patients Treated with 2 g/kg ClairYg (Safety Set, N = 19)

		IGNG 1 g/kg (n = 12)	IGNG 2 g/kg (n = 7)
Platelet count ($\times 10^9/L$)	Mean (SD)	19 (10)	11 (8)
	Median (range)	20 (4-41)	10 (1-22)
Total IgG trough level (g/L)	Mean (SD)	13.26 (5.62)	9.48 (3.12)
	Median (range)	12.15 (7.03-28.50)	10.20 (4.00-13.30)

Table 6. Changes in Serum Creatinine Levels During 30-Day Follow-Up (Safety Set, N = 19)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
N	19	18	17	14	18	15
Median	69.0	66.5	72.0	66.5	71.5	70.0
Range	50.0-126.0	56.0-127.0	49.0-141.0	49.0-102.0	50.0-128.0	59.0-127.0
	Day 7	Day 8	Day 10	Day 12	Day 14	Day 30
N	14	17	15	18	15	18
Median	74.5	72.0	78.0	76.0	72.0	71.5
Range	56.0-146.0	54.0-127.0	51.0-131.0	50.0-132.0	55.0-135.0	51.0-120.0

ed by half in the second week and returned below the threshold for response in the second-week. Patients requiring a second IGNG infusion had lower baseline platelet counts ($10 \times 10^9/L$) than patients with a response after a single infusion ($20 \times 10^9/L$) (Table 5). Relapse of thrombocytopenia, defined as a platelet count below $25 \times 10^9/L$, was reported in 12 of the 16 responders (relapse rate 75%; 95% CI 47.6%-92.7%). Median time to relapse was 21 days (range 7-29).

Twelve (70.6%) of the 17 patients in the efficacy set presented with clinical bleeding signs at baseline (median bleeding score 1 [range 0-8]). Eight (75%) of these patients had their bleeding score reduced to 0 by Day 3. This included the patient with a partial platelet response on Day 5, who had a baseline bleeding score of 8. One of the other 4 patients had a reduction in bleeding score on Day 5 (from score 5 to 1) after a second IGNG infusion. Three of the 4 patients had no change in bleeding score, despite increases in platelet counts. One of these patients remained at a baseline score of 1. The other 2 patients had a baseline score indicative of marked ecchymosis, which is known to take about 1 to 2 weeks to resolve with a progressive resorption and breakdown of bilirubin.

Six (35.3%) of the 17 efficacy set patients required additional ITP therapies. Five (29.4%) patients received corticosteroids that are known to be synergic to IVIg and 3 (17.6%)

patients received another IVIg. Five patients requiring additional ITP therapy were responders to IGNG therapy and 1 patient was a partial responder. All administrations of additional ITP therapies were performed beyond 96 hours after IGNG infusion. The earliest administration was on Day 10.

Safety

Seventeen (89.5%) of the 19 patients in the safety set experienced a total of 45 adverse events. Common ($\geq 10\%$ of patients) adverse events included: fever (9 events in 6 patients, 31.6%), worsening of thrombocytopenia (6 events in 5 patients, 26.3%), headache (5 events in 5 patients, 26.3%), worsening of hypertension (5 events in 4 patients, 21.1%), insomnia, asthenia and nausea (each 2 events in 2 patients, 10.5%). Of the 45 reported adverse events, 16 (36%) were considered related to treatment (pyrexia, headache, nausea, hypertension, chills, and blood creatinine increase): 4 (8.9%) were considered probably related, 10 (22.2%) possibly related and 2 (4.4%) doubtfully related. All adverse events were mild (60.0%) or moderate (40.0%) in intensity. Six (13.3%) adverse events were reported as serious, but none of these were considered related to treatment. Almost all (91.1%) adverse events with a known outcome resolved without sequelae. Of those events that had not resolved by the end of the study, nonwere considered related to treatment.

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Seventeen of the 19 patients (89.5%) in the safety set patients experienced a total of 29 temporally associated adverse events. This corresponded to an incidence per infusion of 1.07. Sixteen temporally associated adverse events in 13 patients were considered related to treatment. These events were pyrexia, headache (each in 5 patients, 26.3%), hypertension, nausea (each in 2 patients, 10.5%), blood creatinine increase and chills (each in 1 patient, 5.3%).

Laboratory assessments revealed good hepatic and renal tolerability, and did not show any evidence that IGNG induced hemolysis. Mild and transient elevations of alanine aminotransferase and/or aspartate aminotransferase were observed in 5 patients. None were considered clinically relevant. One of the 5 patients already had elevated transaminases at baseline, and levels remained above the normal range until the end of the study. In the other 4 patients, elevations were transient and only slightly above the normal range. Serum creatinine remained stable throughout the study (Table 6). Abnormal levels were reported in 5 patients, 1 with known nephroangio sclerosis already had a high creatinine level at baseline and repeatedly demonstrated abnormally high levels throughout the study. Three patients were reported with a single, moderate increase in creatinine, while 1 patient showed a small decrease. None of the reported changes in creatinine were considered clinically relevant or reached the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) criteria for acute renal injury (2-fold increase in serum creatinine or > 50% decrease in glomerular filtration rate [GFR]) [15]. Changes in markers for hemolysis were very limited and isolated, and not consistent for the different hemolytic safety parameters.

No clinically relevant changes in vital signs or physical examinations were observed.

Discussion

In adult patients in the acute phase of chronic ITP, administration of 1 or 2 IGNG infusions at a dose of 1 g/kg provides a rapid increase in platelet count and a decrease in clinical bleeding signs. The majority of patients respond to a single infusion of 1 g/kg. The required cumulative dose (1 or 2 g/kg) to achieve an optimal therapeutic response depended on the patients platelet count at baseline.

The EMA Note for Guidance current at the time of our study required clinical efficacy of IVIg in the acute phase of ITP to be assessed in an open study using standard doses (0.8-1 g/kg on Day 1, which may be repeated once, or 0.4 g/kg/day for 2-5 days) over a few days in at least 15 adult chronic patients with a platelet count of about $20 \times 10^9/L$. The efficacy parameters should include the proportion of patients with a platelet count $\geq 50 \times 10^9/L$, duration of the platelet response, the time to reach a platelet count $\geq 50 \times 10^9/L$, maximum platelet level, and regression of hemorrhages [16]. As IVIg-induced platelet response is known to last for approximately 2 to 4 weeks [1], the efficacy and safety parameters in our study were monitored for a period of 30 days, which covered the expected duration of the IGNG therapeutic effect in ITP.

The patients in our study were considered at risk for bleeding due to a low platelet count or a high bleeding score at baseline. Patients were representative for the general ITP population, although some were in the higher age range. Advanced age has been associated with poorer prognosis [17, 18]. Most patients had been treated for previous episodes of thrombocytopenia. Their previous response to IVIg may be considered as a definite proof of the autoimmune origin of their disease. It does, however, preclude generalization of our findings to an unselected, treatment-naive population. Loss of efficacy of IVIg in ITP patients is rarely seen.

The response to IGNG infusion in our study was high (94.1%). The one patient with a partial platelet response had an increase in platelet count from $10 \times 10^9/L$ at baseline to $36 \times 10^9/L$ on Day 5, while her bleeding score decreased from 8 to 0 within 3 days after IGNG infusion. This patient can therefore be considered a clinical responder and shows that platelets count above $25 \times 10^9/L$ decreases the risk of bleeding. It is also of interest that the 6 patients in our study who had previously undergone splenectomy remained sensitive to IVIg and were responders to IGNG therapy. The fast onset of action of IGNG further adds to its beneficial features in a patient population requiring quick response, specifically in situations with risk of bleeding.

The evolution of platelet counts in our study was in agreement with what is known about the

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transient effect of IVIg: a therapeutic response within a few days, a peak response within a week and a gradual decrease in response with high inter-individual variability thereafter. The high inter-individual variability is probably indicative for the severity of underlying disease. The pattern of thrombocytopenia relapse was as expected on the basis of the duration of action of immunoglobulin. The reduction in bleeding scores and the need for additional ITP therapies were consistent with the evolution of platelet counts.

The observed types, frequencies and severity of adverse events and those potentially related to IGNG did not suggest an increased risk for adverse events other than those typically associated with IVIg products [19-21]. IGNG demonstrated good safety, including good renal and hepatic tolerance, and did not induce hemolytic events, despite the relatively high cumulative doses and the presence of other risk factors such as high age (60 years and older) and existing pre-morbid conditions. The absence of hemolytic events supports the objective pursued in the manufacturing process of IGNG, namely the inclusion of selective affinity chromatography to eliminate any anti-A and anti-B hemagglutinins to reduce the risk of hemolytic events.

The results of our study demonstrate that IGNG is effective and safe in adult patients with confirmed ITP who have previously been treated successfully with another IVIg product. The majority of patients responded to a single dose of 1 g/kg. IGNG rapidly increased platelets counts and showed a potential to produce rapid reduction in bleeding risk and resolution of hemorrhagic signs resulting from low platelet count or high bleeding score. The response to IGNG is in keeping with the known profile of IVIg therapy in chronic ITP. Patients with more profound thrombocytopenia may benefit more from higher doses. IGNG was safe and generally well tolerated, with no signs of hemolysis or negative impact on renal and hepatic function.

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Disclosure of conflict of interest

Bertrand GODEAU served as expert for AMGEN, NOVARTIS, LFB, Roche and ARGENX, and received fund for research from Roche.

Address correspondence to: Bertrand Godeau, Department of Internal Medicine, University Hospital Henri Mondor, France. Tel: +33 14981 29 05; Fax: +33 149 81 29 02; E-mail: bertrand.godeau@aphp.fr

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