Treatment of Adult Chronic Autoimmune Thrombocytopenic Purpura With Repeated High-Dose Intravenous Immunoglobulin

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Intravenous (IV) infusions of Ig concentrates are an effective but expensive treatment for patients with autoimmune thrombocytopenic purpura (AITP). The optimal treatment protocol and the long-term results are uncertain, and the precise mechanism by which the platelet count increases is poorly understood. Twenty adult patients with chronic AITP were enrolled in a prospective study to compare the respective efficacy of two high-dose IVIgG induction regimens (1 g *v* 2 g/kg body weight) and the long-term effect of six 1 g/kg body weight IVIgG reinfusions. An initial response was observed in all 18 evaluable patients: the platelet count increased to a mean value of 251 × 10^9/L (range 72 to 836 × 10^9/L) and the mean pretreatment platelet count was multiplied by 14.6. No difference in efficiency was observed between the two IVIgG dosages. The degree of the platelet count increment correlated in both groups with the increase in the clearance of antibody-coated red blood cells, measured by an isotopic method, but not with the serum IgG elevation. Treatment was considered to have failed in 11 patients, 90 days after the last IVIgG reinfusion (D90), because the platelet counts were comparable with pretreatment values. In contrast, a complete response was observed at D90 in five patients (mean platelet count: 184 × 10^9/L; range: 150 to 250 × 10^9/L) and a partial response at D90 was obtained in the remaining two patients (platelet counts: 70 and 104 × 10^9/L). Five of the 7 responders at D90 kept a platelet count above 50 × 10^9/L during the entire follow-up period (mean 33 months; range: 5 to 66) with no further treatment; unfortunately, no clinical or biologic criteria were found to be predictive of the long-term response. This study shows that an IVIgG infusion regimen of 1 g/kg body weight could safely replace the classical 2 g/kg body weight dosage, at least in patients who do not have life-threatening thrombocytopenia. Moreover, repeated IVIgG reinfusion could be an alternative for AITP patients in whom splenectomy is contraindicated.

SINCE THE first report by Imbach et al,[1] several studies have confirmed that high-dose intravenous immunoglobulin G (IVIgG) infusions are effective in the treatment of patients with autoimmune thrombocytopenic purpura (AITP).[2] After a total infusion of 2 g of IVIgG/kg body weight, the platelet count transiently increases in 70% to 100% of patients. However, the precise platelet response mechanism has not yet been entirely established[3] and the exact place of such treatment in the management of these patients is controversial, in particular because of its higher cost. There is general agreement that IVIgG should be administered in emergency situations and that it is a safe preparation for surgery.[4] In contrast, the ability of the treatment to cure chronic AITP is controversial, even if repeated IVIgG infusions have been proposed as maintenance treatment[5,6] and have occasionally given persistent remissions.[5,7-10] We report the results of treatment with repeated IVIgG infusions in 20 adult patients with chronic AITP. This randomized open trial was conducted to determine: (1) the respective efficiency of two IVIgG infusion regimens, ie, 1 g *v* 2 g/kg body weight; (2) the long-term outcome of patients treated with repeated IVIgG infusions and the ability of the treatment to avoid splenectomy; and (3) clinical and biologic characteristics with predictive value for treatment efficacy.

PATIENTS AND METHODS

Patients

Twenty consecutive adult patients with chronic AITP were included in a randomized open prospective study. The patients were informed of the nature of the trial and its attendent risks in the presence of an independent witness, and all gave their informed consent. AITP was diagnosed according to standard criteria, ie, isolated thrombocytopenia, normal or increased megacaryocyte count in an otherwise normal bone marrow (BM) aspirate, and absence of other causes of thrombocytopenia. The eligibility criteria were as follows: no diseases known to be associated with AITP (ie, human immunodeficiency virus (HIV) infection, systemic lupus erythematosus and other connective tissue disorders, lymphoproliferative disorders, thyroid or liver diseases); no treatment for at least two weeks before the study; a stable, low platelet count (less than 50 × 10^9/L); and no life-threatening hemorrhagic syndrome. Because one goal was to test the ability of the treatment to avoid splenectomy, we included nonsplenectomized patients only 4 months after the diagnosis of AITP. However, the analysis of patient histories clearly showed that they had chronic AITP. Thus, the mean time between the date of diagnosis and the last observed abnormal platelet count was 30 months, and all the patients had thrombocytopenia for more than 6 months (range 9 to 87 months), which is the time commonly used to affirm that AITP is chronic.[11]

IVIgG Preparation and Treatment Schedules

Unselected lots of commercially available IVIg (Biotransfusion, Roissy, France) were used. They contained more than 98% of unmodified human IgG and were obtained by Cohn ethanol fractionation with treatment at pH 4 in the presence of trace amounts of pepsin.[12]

Initial treatment. The patients were randomized to receive initially a total IVIgG dose of 1 g/kg body weight (group A) or 2 g/kg body weight (group B) as two divided doses on two consecutive days in both cases. The daily IVIgG dose was administered in 4 to 8 hours according to tolerance. Platelet counts were measured on days 1 (pretreatment), 2, 3, 4, 5, 6, 11, 15, and weekly thereafter.

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Table 1. Pretreatment Characteristics of the Patients

	Group A	Group B	
No. of patients	9	9	
Mean (range) age (yrs)	45 (19-70)	48 (22-84)	NS
Sex ratio (M/F)	5/4	5/4	
Mean (range) and median interval between diagnosis and IVIgG (mos)	8 (4-13)	8 (4-15)	NS
	7	7	
Mean (range) and median off-therapy duration at initiation of IVIgG (wks)	8 (2-24)	18 (3-40)	NS
	4	10	
Mean (range) and median platelet count before IVIgG ($\times 10^9$/L)	29 (4-45)	19 (8-47)	NS
	34	12	
Mean (range) and median serum IgG value before IVIgG (g/L)	10.4 (3.6-24.5)	10.3 (8.2-12.7)	NS
	10	9.9	
Previous corticosteroid response:			
No response	4	4	NS
Dependence	5	5	
Number of patients with positive PIFT	4	7	NS
Number of patients with positive PIIFT	5	5	NS

Group A: patients initially treated with a total dose of 1 g of IVIgG/kg body weight. Group B: patients initially treated with a total dose of 2 g of IVIgG/kg body weight. Only IgG antibodies were determined in immunofluorescence tests.

Abbreviation: NS, no statistical difference between the groups.

The initial response was considered complete when the platelet count increased above 150×10^9/L and partial if it increased above 50×10^9/L and at least twice the initial count; treatment was considered to have failed in the other cases.

IVIgG reinfusions. The first IVIgG booster (1 g/kg body weight in both groups) was administered when the platelet count fell below 50×10^9/L; five other reinfusions (total of six boosters) were administered at the same dosage, every 2 to 3 weeks, unless a stable normal platelet count ($>150 \times 10^9$/L) was obtained or the response was exhausted.

Long-term results were evaluated 90 days (D90) after the last IVIgG booster, as follows: failure, when the platelet response was exhausted or only a transient response to each IVIgG infusion was observed; complete response, if the D90 platelet count was above 150×10^9/L; partial response, if the D90 platelet count was between 50 and 150×10^9/L and more than twice the initial platelet count. In addition, platelet counts were evaluated for 5 to 75 months (mean, 40 months) after the last IVIgG infusion on the occasion of return visits to the hospital.

Clinical and Biologic Correlations

Several parameters were studied in an attempt to identify correlations with the response to IVIgG infusions, as follows: age, sex, duration of disease before IVIgG treatment, response to previous steroid treatment, presence of detectable IgG platelet antibodies, ability to block the reticuloendothelial system, and IgG serum levels before and two days after the initial IVIgG infusions. Platelet antibodies were determined by means of the platelet direct (PIFT) and indirect (PIIFT) immunofluorescence tests according to the techniques described by Borne et al,[13,14] before and 2 days after the initial IVIgG treatment, using an anti-IgG antiglobulin (Dakopatts, Copenhagen, Denmark). The ability to block the reticuloendothelial system was determined in the 15 evaluable rhesus$^+$ patients immediately before and 24 hours after completion of IVIgG therapy and in nine healthy rhesus$^+$ control subjects, by analyzing clearance of antibody-coated red blood cells (RBCs) according to the method described by Frank et al.[15] Briefly, 10^9 autologous RBCs in 1 mL of physiologic saline were labeled with 50 microCi (37×10^3 Bq) of 51Cr (Amersham, Les Ullis, France). The RBCs were then washed three times in saline and incubated with 40 μg of anti-D IgG (Centre National de Transfusion Sanguine, Paris, France) at 37°C for 60 minutes. After being washed twice, the RBCs were resuspended in 2 mL of saline and reinjected. Clearance was studied by counting 2 ml of each venous blood sample collected 10, 20, 30, 45, 60, and 90 minutes after the injection in a gamma counter. The half life of sensitized RBCs (T1/2) was determined using a monoexponential function. The RBC T1/2 in the nine control subjects was 22.9

Table 2. Initial Response After IVIgG Infusions

Patient/ Group	Interval Between Diagnosis and IVIgG (mos)	Plt Count (10^9/L) Before IVIgG	Plt Count (10^9/L) After First IVIgG	RBC Survival (T1/2) (mn) Before IVIgG	RBC Survival (T1/2) (mn) After First IVIgG
1 A	13	12	450	21	29
2 A	12	45	465	55	95
3 A	8	37	120	23	27
4 A	7	40	150	25	36
5 A	5	34	260	35	43
6 A	7	4	250	16	23
7 A	5	20	238	16	17
8 A	4	30	175	35	37
9 A	12	35	100	21	25
10 B	15	31	286	26	45
11 B	4	10	72	ND	
12 B	4	8	145	17	25
13 B	10	12	273	33	34
14 B	5.5	8	85	15	22
15 B	11	47	836	35	70
16 B	6	11	161	ND	
17 B	7	23	185	ND	
18 B	11	20	275	40	60

Group A: patients initially treated with a total dose of 1 g of IVIgG/kg body weight. Group B: patients initially treated with a total dose of 2 g of IVIgG/Kg body weight. RBC survival is the half life (T1/2) of autologous-labeled, antibody-coated RBCs.

Abbreviations: mn, minute; Plt, platelet; ND, not determined (negative rhesus patients).

Table 3. Initial Response After IVIgG Infusions

	Group A	Group B	
No. of patients	9	9	
Mean (range) and median maximum platelet count (10^9/L)	245 (100-465)	258 (72-836)	NS
	238	185	
Response*			
Complete	7	6	
Partial	2	3	NS
Failure	0	0	
Mean (range) and median time to reach maximum platelet count (ds)	7 (4-10)	6 (4-11)	NS
	5	6	
Mean (range) and median time platelet count > 50 × 10^9/L after first IVIgG infusion (ds)	35 (7-90)	25 (8-96)	NS
	23	14	
Mean (range) and median percentage increase in IgG level after IVIgG	161 (55-336)	227 (160-322)	$P < .05$
	141	225	
Mean (range) and median RBC survival before IVIgG ($T^1/_2$) (mins)	27 (16-55)	28 (17-40)	NS
	23	26	
Mean (range) and median percentage increase in RBC survival after IVIgG	30 (6-73)	53 (3-100)	NS
	23	47	

Group A: patients initially treated with a total dose of 1g of IVIgG/kg body weight. Group B: patients initially treated with a total dose of 2 g of IVIgG/kg body weight. RBC survival is the half-life ($T^1/_2$) of autologous-labeled antibody-coated RBCs.

Abbreviation: NS, no statistical difference between the groups.

* Treatment response was considered complete if platelet count increased above 150 × 10^9/L, partial if platelet count increased above 50 × 10^9/L, and at least twice the initial level, and failure in the other cases.

± 5.8 minutes.[16] The differences observed between our results and those previously published[17-19] concerning this value in control subjects and the degree of increase in antibody-coated RBC survival after IVIgG infusions (see after) were probably caused, on the one hand, by the amount and characteristics of the anti-D antibody used and, on the other hand, to the date of the study after IVIgG infusions; indeed, Bussel et al[18] showed that maximum Fc receptor blockade was obtained 8 days after the start of IVIgG infusions.

Statistical Analysis

Quantitative values were compared using Fisher's exact test and mean values using the Mann and Whitney U test. Linear regression analysis were used to compare quantitative parameters in the two randomized groups. A P value of .05 or less was considered significant.

RESULTS

Twenty patients (11 males, 9 females) were enrolled in the study but only 18 were evaluable (Table 1): one patient (group A) subsequently developed systemic lupus erythematosus and another (group B) experienced severe intolerance (general discomfort, chills and hyperthermia) immediately after the first IVIgG infusion. No IgA antibody was found in this latter patient, who refused subsequent IVIgG infusions. As shown in Table 1, the patients' characteristics were similar in groups A and B. All the patients had previously been treated with corticosteroids; one patient had also received danazol (patient [pt] 5) and another vincristine (pt 1).

Severe intolerance was only observed in one patient (mentioned above), but transient and minor side effects developed in 12; they included headache (n = 8), chills (n = 6), fever (n = 2), myalgia (n = 2), abdominal pain and vomiting (n = 1), and a urticarial rash (n = 1).

Immediate Response to IVIgG Infusions

An initial response was observed in all 18 evaluable patients (complete response in 13, partial response in 5) (Table 2). The platelet count increased to a mean value of 251 × 10^9/L (range 72 to 836 × 10^9/L) and the pretreatment platelet counts were multiplied by 14.6 (range 2.9 to 62). The maximum platelet count was observed 4 to 11 days (mean

Table 4. Long-Term Response After IVIgG Infusions

Pts/ Gr	Interval Between Diagnosis and IVIgG (mos)	D90 Plt Count 10^9/L	Last Evaluable Plt Count (10^9/L) Without Other Treatment (time after the last IVIgG infusion)	Subsequent Treatment(s) (results)
1/A	13	10	10 (3 mos)	spln (pCR)
2/A	12	150	>150 (36 mos)	0
3/A	8	15	15 (3 mos)	spln (pCR)
4/A	7	24	24 (3 mos)	spln (pCR)
5/A	5	30	30 (30 mos)	0
6/A	7	10	15 (10 mos)	0
7/A	5	25	25 (3 mos)	spln (pCR)
8/A	4	70	>50 (32 mos)	0
9/A	12	104	>100 (5 mos)	0
10/B	15	250	>50 (66 mos)	0
11/B	4	24	24 (3 mos)	spln (tCR)
12/B	4	170	20 (relapse) (22 mos)	IVIgG (tCR), spln (pCR)
13/B	10	150	27 (relapse) (14 mos)	spln (pPR)
14/B	5.5	5	5 (3 mos)	spln (NE)
15/B	11	200	>50 (27 mos)	0
16/B	6	30	30 (3 mos)	danazol (pCR)
17/B	7	20	30 (23 mos)	0
18/B	11	5	5 (3 mos)	danazol (pCR)

Group A: patients initially treated with a total dose of 1 g of IVIgG/kg body weight. Group B: patients initially treated with a total dose of 2 g of IVIgG/Kg body weight. D90 platelet count represented the patient platelet count 90 days after the last IVIgG booster.

Abbreviations: CR, complete response; Gr, group; NE, non evaluable; plt, platelet; PR, partial response; Pts, patients; spln, splenectomy; p, permanent CR or PR; t, transient CR or PR.

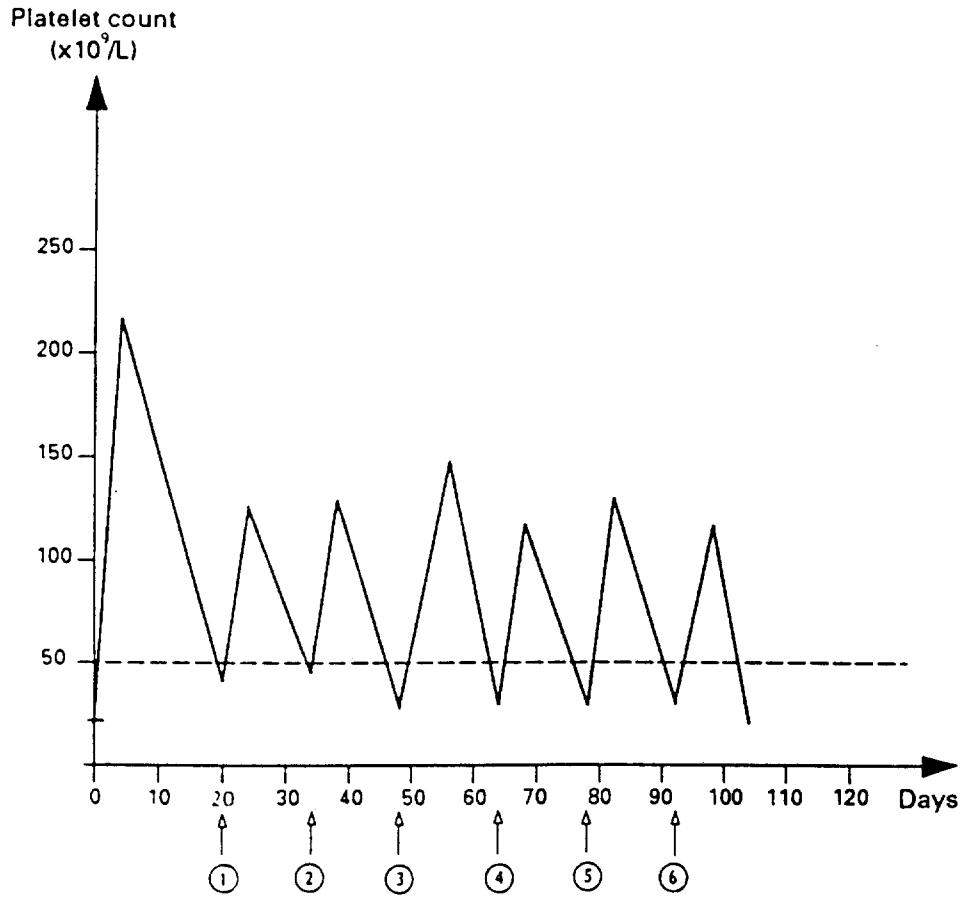

Fig 1. Mean pre- and post-IVIgG platelet counts in eight patients with transient responses after IVIgG readministrations. ↑ indicates IVIgG administrations.

and median: 6 days) after the first IVIgG infusion. The mean time required to reach a platelet count above 150 × 10^9/L in the 13 patients with complete responses after initial IVIgG infusions was 4 days (range 2 to 6; median value: 4 days). The mean percentage increase in the serum IgG concentration was significantly higher in group B (227%) than in group A (161%) ($P < .05$) but, surprisingly, there was no difference in the platelet count increment between the two groups (Table 3). In addition, the platelet count increment correlated well with the increase in the antibody-coated RBC survival in both groups ($r = .704$ in groups A and B [$P < .01$]; .609 in group A [$P < .01$]; .718 in group B [$P < 0.01$]). In contrast, none of the following factors correlated with the platelet count increment: sex, age, duration of the disease before IVIgG infusions, response to corticosteroid treatment, presence before or evolution after treatment of IgG platelet antibodies, and percentage increase in serum IgG concentration after IVIgG infusion.

IVIgG Reinfusion

Thirteen of the 18 evaluable patients received the six IVIgG boosters as planned. The other five patients received only one (n = 3) or two boosters (n = 2) because of an exhaustion of the response to IVIgG infusions in three (pts 11, 16, and 18), and a prolonged complete response in two (pts 2, 10).

The long-term responses were considered as failures in 11 patients (Table 4). Patients 11, 16, and 18, all in group B, became refractory to IVIgG reinfusions (see above) and only a transient response was observed in the other eight (pts 1, 3, 4, 5, 6, 7, 14, 17), six of whom were in group A. Figure 1 shows the mean pre- and post-IVIgG platelet counts in these eight patients; the mean D90 platelet count was 17 × 10^9/L (median value: 15 × 10^9/L), a value comparable with the mean pretreatment count (22 × 10^9/L) (median value: 20 × 10^9/L). Six of these 11 patients (pts 1, 3, 4, 7, 11, and 14) subsequently underwent splenectomy; a persistent complete response was obtained in four (pts 1, 3, 4, and 7) (mean follow-up: 40 months; range 24 to 60 months), and a transient response in one (pt 11); the last patient (pt 14) was lost to follow-up after an initially successful splenectomy. Two other patients (pts 16 and 18) achieved a complete response on danazol treatment. No further treatment was administered to the remaining three patients (pts 5, 6, and 17), in whom the platelet count remained between 15 and 30 × 10^9/L without bleeding complications (mean follow-up after the last IVIgG infusion: 21 months; range 10 to 30 months).

A complete response at D90 was observed in five patients (mean platelet count at D90: 184 × 10^9/L; range 150 to 250), and a partial response in two others (70 × 10^9/L and 104 × 10^9/L) (Table 4). Two of the patients (pts 2 and 10)

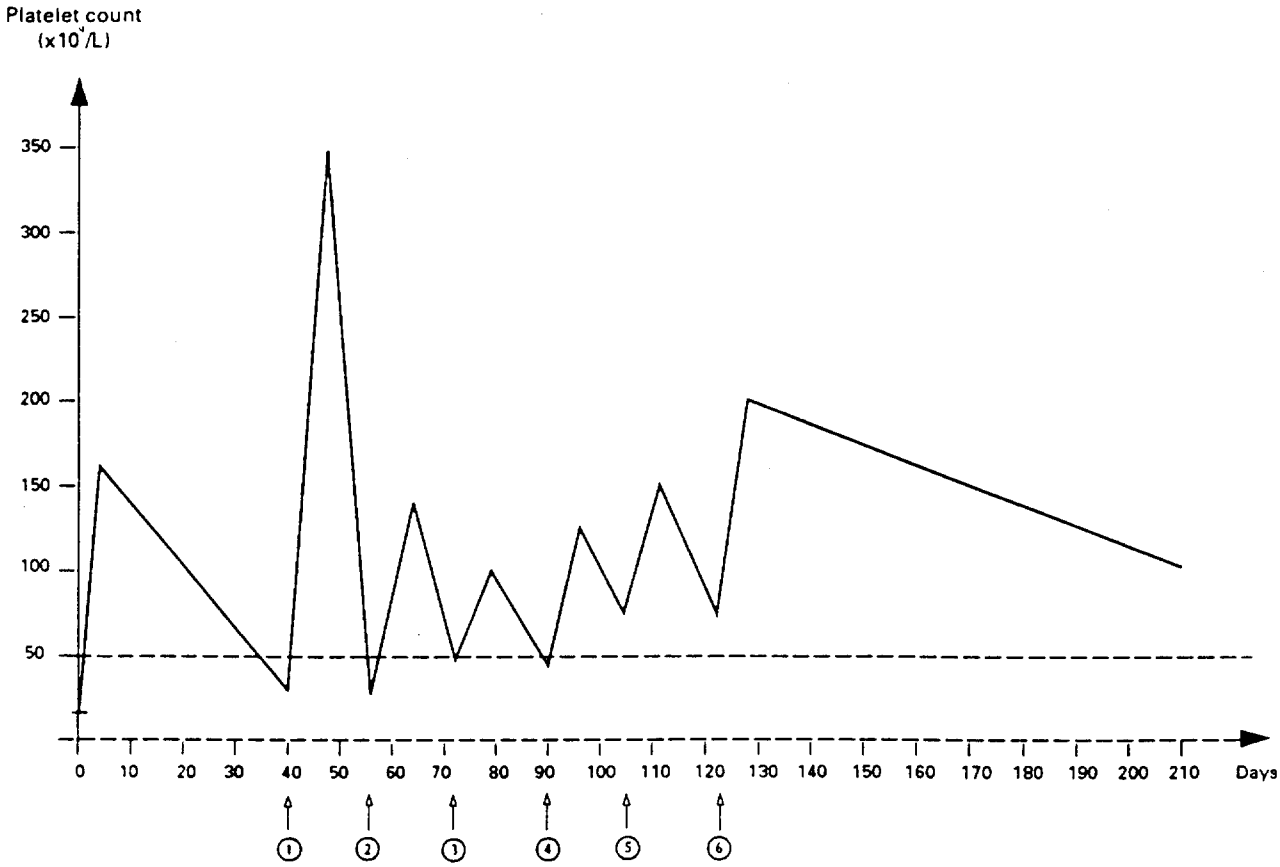

Fig 2. Mean pre- and post-IVIgG platelet counts in the five patients with complete or partial response after the six IVIgG readministrations. ↑ indicates IVIgG administrations.

achieved a complete response with only one booster. The platelet count decreased to about 50 × 10^9/L 18 months later in patient 10 and then remained stable without treatment for the following 48 months. The complete remission persisted in the other patient (pt 2), 36 months after the last IVIgG administration. Six IVIgG boosters were required in the remaining five responders (three complete responses and two partial responses); the platelet counts improved gradually during treatment with IVIgG boosters (Fig 2). Three patients (pts 8, 9, and 15) were still in partial remission at the last hospital visit, 5, 27 and 32 months after the last IVIgG infusion. A relapse occurred 22 months after the last IVIgG booster in another patient (pt 12) (described by Bierling et al[7]). Multiple IVIgG reinfusions led to a further complete remission lasting 11 months. The patient finally underwent successful splenectomy. A relapse occurred 14 months after the last IVIgG booster in the remaining patient (pt 13), who also underwent splenectomy but with only a partial response.

None of the patients' characteristics listed in Table 5, nor the presence before or the evolution after IVIgG treatment of platelet antibodies correlated with the long-term response, although the first IVIgG infusion tended to procure a more important platelet count increment and more durable effect in the long-term responders.

DISCUSSION

It is well established that IVIgG is an effective treatment for AITP but its precise place in the management of these patients is controversial, particularly on account of its high cost. Furthermore, more than 10 years after the first demonstration of its efficacy, the optimal dosage of IVIgG, together with the best timing of the infusions, and their long-term efficacy remain uncertain. Lastly, the precise mechanism of the platelet increment is unknown. Our results provide answers to some of these questions.

As previously reported by others,[20,21] we found that a two-day administration regimen rapidly increased the platelet count and was well tolerated, even if minor side-effects were frequent. Importantly, a total infusion of 1 g IVIgG/kg body weight was as efficient as the 2 g/kg regimen initially proposed by Imbach et al.[1] However, there are several difficulties in extrapolating these results. In particular, although Bussel et al[6,20] also failed to find a significant difference between the platelet count increment and the amount of infused IVIgG, the existence of a correlation has been suggested in sporadic reports[17,22] and a series of patients.[23] Furthermore, the lower dosage has been reported to be ineffective and a higher dosage effective in selected patients, both with other preparations of IVIgG[24,25] and with the

Table 5. Characteristics of the Patients in Terms of Long-Term IVIgG Efficacy

	Long-Term Responders*	Long-Term Nonresponders*	
No. of patients	7	11	
Sex ratio (M/F)	4/3	6/5	NS
Mean (range) age (yrs)	49 (22-70)	45 (19-84)	NS
Group A *v* group B	3/4	6/5	NS
Mean (range) and median interval between diagnosis and IVIgG (mos)	10 (4-15)	7 (4-13)	NS
	11	7	
Mean (range) and median platelet count before IVIgG ($\times 10^9$/L)	30 (8-47)	20 (4-40)	NS
	31	20	
Mean (range) and median peak platelet count after first IVIgG infusion ($\times 10^9$/L)	326 (100-836)	204 (72-450)	NS
	273	185	
Mean (range) and median time platelet count > 50 × 10^9/L after first IVIgG infusion (ds)	50 (10-96)	17 (7-31)	NS
	35	15	
Mean (range) and median RBC survival before IVIgG (mins) ($T^1/_2$)	32 (17-55)	24 (16-40)	NS
	33	21	

Group A: patients initially treated with a total of 1 g of IVIgG/kg body weight. Group B: patients initially treated with a total of 2 g of IVIgG/kg body weight. RBC survival is the half life ($T^1/_2$) of autologous-labeled antibody-coted RBCs.

Abbreviation: NS, no statistical difference between the groups.

* Long-term responders are patients with partial or complete response at D90 post-IVIgG (platelet count above 50 × 10^9/L and twice the initial level); nonresponders are the remainders.

same preparation as that used in this study (personal results). However, it is difficult to compare our results with others because the amount infused and the manufacturer of IVIgG concentrates, as well as the characteristics (acute or chronic) of AITP are different. Indeed, chronic AITP had been diagnosed a relatively short time previously in our patients, who did not have life-threatening hemorrhagic conditions and IVIgG has been reported to be more effective when treatment is started at an early stage of the disease.[3,22] Thus, further studies are required before the reduced IVIgG dosage can be proposed for all AITP patients, particularly those with life-threatening conditions or long-standing AITP.

Our results also confirm the ability of IVIgG treatment to procure prolonged remission after repeated booster infusions (7 of 18 patients). These favorable long-term results were probably not caused by spontaneous remissions, because our patients presented well-defined chronic AITP,[11] as evidenced by the presence of immune platelet destruction over at least a 9-month period in all the evaluable patients, and because spontaneous remissions are very rare in chronic AITP.[4] This assumption is also supported by the gradual increase in the platelet count during IVIgG reinfusion in 5 of the 7 long-term responders. Unfortunately, no factors predictive of a favorable prolonged response were identified, although the response after the first IVIgG infusion was stronger and slightly longer in the long-term responders. In view of these results, as it has been yet reported in a group of drug-resistant splenectomized patients,[5] repeated IVIgG infusions may be a safe alternative when splenectomy is contra-indicated.

The precise mechanism involved in the platelet count increment after IVIgG infusions has not yet been established. There is evidence that Fc receptor blockade, leading to a prolongation of the clearance time of circulating immune particles, may at least partly explain the immediate platelet response.[17] Indeed, we found a correlation between the degree of Fc receptor blockade (estimated by evaluating of the clearance of antibody-coated RBCs) and the intensity of the platelet response. The quantity of IVIgG necessary to obtain this blockade is unclear, because the IVIgG dosage proposed empirically by Imbach et al[1] is usually administered. Our results, showing that comparable Fc receptor blockade was obtained with the 1 g/kg and 2 g/kg body weight IVIgG regimens, and that the intensity of blockade did not correlate with the increase in the serum IgG concentration, could explain the similar platelet response obtained with the two dosages. Other mechanisms, particularly an idiotypic interaction,[26,27] could account for the prolonged responses in some patients, because Fc receptor blockade probably does not persist when injected IVIgG is no longer present in the circulation. Unfortunately, platelet antibody studies provided no predictive markers of the long-term outcome, or further arguments to support this hypothesis.

In conclusion, our findings suggest that when IVIgG treatment is required for chronic AITP patients, a 1 g/kg body weight regimen administered in 1 or 2 days can safely replace the usual 2 g/kg regimen. However, further studies are necessary to confirm that this reduced regimen is always effective and to determine its suitability for patients with life-threatening conditions. Our results also confirm that repeated IVIgG infusions can sometimes cure chronic AITP. Because the response is unpredictable and usually partial, and as the cost of IVIgG is high, repeated IVIgG infusions should, in our opinion, only be proposed for patients in whom splenectomy is contra-indicated.

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