Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial

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Summary

Background Treatment of adults with autoimmune thrombocytopenic purpura (AITP) is based more on individual experience than on results of controlled studies. We compared intravenous immunoglobulin with high-dose methylprednisolone in untreated adults with severe AITP and assessed efficacy of subsequent oral steroids compared with placebo. Primary outcome was number of days with platelet count greater than 50×10^9/L within the first 21 days.

Methods We did a randomised multicentre trial based on a 2×2 design. 122 adults with severe AITP (platelet count $\leqslant20\times10^9$/L) were randomly assigned to receive either intravenous immunoglobulin or high-dose methylprednisolone on days 1–3 (randomisation A), and then to receive either oral prednisone or placebo (randomisation B) on days 4–21. Analysis was by intention to treat.

Findings Six patients were excluded from the analysis. The number of days on which platelet counts were above 50×10^9/L was 18 in 56 patients receiving intravenous immunoglobulin and 14 in 60 receiving high-dose methylprednisolone (p=0·02). Percentage of patients who had platelet counts over 50×10^9/L on days 2 and 5 was 7% and 79%, respectively, in the intravenous immunoglobulin group compared with 2% and 60%, respectively, in the high-dose methylprednisolone group (p=0·04). During the second treatment period, prednisone was more effective than placebo for all short-term endpoints. Patients who received intravenous immunoglobulin and prednisone had platelet count greater than 50×10^9/L for 18·5 days (p=0·005), and those treated with high-dose methylprednisolone and prednisone had this count for 17·5 days.

Interpretation Intravenous immunoglobulin and oral prednisone seems to be more effective than high-dose methylprednisolone and oral prednisone in adults with severe AITP, although the latter treatment is effective and well tolerated.

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See Commentary page 4

Introduction

People with severe autoimmune thrombocytopenic purpura (AITP) are at risk of life-threatening bleeding and therefore require a treatment whose effects are ideally rapid, reliable, and sustained. The best treatment for adults with newly diagnosed AITP is controversial.[1,2] Oral steroids (1–2 mg per kg bodyweight per day) are the usual initial treatment for adults with symptomatic thrombocytopenia. Results of uncontrolled studies suggest that the platelet count rises to more than 50×10^9/L in two-thirds of patients thus treated, but only after about 1 week.[1,2] Imbach and colleagues[3] first noted that intravenous immunoglobulin infusions (2 g/kg bodyweight) rapidly increase the platelet count in children. These results were subsequently confirmed in adults, and intravenous immunoglobulin is now a frequent first-line treatment for patients with severe AITP.[1,4–6] However, the exact role of intravenous immunoglobulin in adults with severe AITP is controversial, mainly because of the transient efficacy and high cost of this treatment.[7,8] Very-high-dose steroids can lead to a more rapid rise in platelet count in childhood AITP than conventional doses, albeit with the side-effects of high-dose methylprednisolone in children, which include hypertension, hyperglycaemia, and circulatory complaints.[9–14] Rapid but transient responses to high-dose methylprednisolone have also been reported in adults, including some patients resistant to intravenous immunoglobulin.[15–18] Furthermore, high-dose methylprednisolone is cheaper than intravenous immunoglobulin, and preliminary reports suggest that tolerability in adults is satisfactory.[15,16,18]

In 1994, a panel of experts commissioned by the American Society of Hematology identified the need for rigorous trials to assess the respective roles of treatments currently used to treat AITP.[2] Despite the absence of controlled studies, the panel of experts stated that, in view of the potentially serious consequences of severe AITP, treatment with high-dose parenteral steroids and intravenous immunoglobulin was justified, either alone

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or in combination, together with transfusions of platelets for life-threatening bleeding.[2]

We therefore did a randomised multicentre trial with two main aims: to compare response to a 3-day course of either intravenous immunoglobulin or high-dose methylprednisolone in untreated adults with severe AITP and a platelet count below 20×10^9/L; and to assess the efficacy of a subsequent 18-day course of oral steroids compared with placebo. A secondary aim was to record the effect of treatments on long-term outcome.

Patients and methods

Patients

Patients were recruited from 27 haematology and internal-medicine units in France. Patients were eligible for the study if they had: a diagnosis of AITP during the 4 weeks before study entry; age over 16 years and under 75 years; and a platelet count of 20×10^9/L or less. AITP was diagnosed in accordance with standard criteria,[1] which comprised isolated thrombocytopenia; a normal or raised megakaryocyte count in an otherwise normal bone-marrow aspirate; no other disease known to be associated with immune thrombocytopenia, such as HIV infection, lymphoproliferative disorders, thyroid or liver disease, and definite systemic lupus erythematosus ($\geqslant$4 American Rheumatism Association criteria);[19] and no treatment with drugs known to induce thrombocytopenia. Patients were not eligible if they had received any treatment known to be effective for AITP or if they presented with life-threatening gastrointestinal haemorrhage or haemorrhage of the central nervous system. Patients were also not eligible if they had known contraindications to intravenous immunoglobulin (eg, kidney failure, defined by a creatinine concentration in serum exceeding 120 μmol/L) or to high-dose methylprednisolone (eg, uncontrolled diabetes mellitus; uncontrolled gastroduodenal ulcer; a history of heart disease; or cardiac arrhythmia, cardiac conduction disorders, or concomitant treatment with anti-arrhythmic agents).

We assessed severity of the haemorrhagic syndrome at onset with a clinical scoring system that adds up individual scores for the following items (best possible score, 31): cutaneous purpura (localised, 1; extensive, progressive, or both, 3; associated with large ecchymoses, 4); haemorrhagic oral bullae, spontaneous gingival bleeding, or both (4); epistaxis (unilateral, 2; bilateral, 3); macroscopic haematuria (5); overt gastrointestinal haemorrhage (5); major menorrhagia, metrorrhagia, or both (4); bleeding on the fundus oculi in the absence of other causes (5); and age over 60 years (1).

The trial was approved by the ethics committee of Henri Mondor Hospital (Créteil, France). It was done in accordance with the Helsinki Declaration and Good Clinical Practice. Informed written consent was obtained from all participants.

Study protocol

We randomly assigned patients at diagnosis to one of four management strategies in accordance with a factorial (2×2) design. Simultaneous double randomisation was done by centralised telephone assignment stratified by centre, and was based on random permuted blocks (the size of which was unknown to the investigators). First, we randomly assigned patients to receive either intravenous immunoglobulin (0·7 g per kg bodyweight per day; Gammagard SD, Baxter Bioscience, Glendale, CA, USA) or high-dose methylprednisolone (15 mg per kg bodyweight per day, total daily dose <1 g; Solumedrol, Upjohn/Pharmacia, North Peapack, NJ, USA) in an open fashion from day 1 to day 3 (randomisation A). Patients were then randomly assigned either oral prednisone (10 mg tablets, 1 mg per kg bodyweight per day) or an identical placebo in a masked fashion from day 4 to day 21 (randomisation B). Intravenous immunoglobulin was infused at a dose rate of 0·2 g per kg bodyweight per h and methylprednisolone over at least 3 h, in 500 mL of 5% glucose solution. Oral prednisone and placebo were gradually withdrawn after day 21, by 10 mg/day. Patients were not intended to receive any other treatment; however, if serious haemorrhagic syndrome (haemorrhagic score >5) occurred after day 5, patients could be switched to another treatment, and the scheduled treatment was judged to have failed.

Procedures

We measured platelet counts daily up to day 8—or up to day 21 if they remained below 50×10^9/L—and three times a week from day 8 to day 21 if they exceeded 50×10^9/L. Thereafter, we counted platelets at least every week from day 21 to day 45, and monthly from day 45 to month 12.

We measured short-term (within the first 21 days after randomisation) and long-term (within the first 12 months of randomisation) outcomes. The primary (short-term) outcome measure was number of days with a platelet count greater than 50×10^9/L. Secondary short-term outcome measures were: treatment response on day 21 (see below); number of days with platelet counts greater than 20×10^9/L and twice the baseline count within the first 21 days; percentage of patients with platelet counts exceeding 20×10^9/L and 50×10^9/L on days 2, 3, 4, and 5; mean platelet count on days 2–5; highest platelet count between day 1 and day 21; and time to treatment switches. Secondary long-term outcomes were treatment response at month 12 and time to treatment failure.

Treatment response on day 21 was classified in accordance with platelet count, as follows: complete response if platelet count above 150×10^9/L; partial response if platelet count between 50×10^9/L and 150×10^9/L; minor response if platelet count between 20×10^9/L and 50×10^9/L and at least twice the baseline count; and failure in all other cases, and when patients received a treatment other than that assigned by randomisation (ie, a treatment switch). Treatment response at 12 months was similarly defined, except that minor responses (defined above) were deemed failures.

Sample-size calculation

The main outcome measure was number of days with a platelet count greater than 50×10^9/L within the first 21 days after randomisation. However, owing to absence of published data on this outcome, we based sample size calculation on the first secondary outcome measure—ie, treatment response (complete and partial) on day 21. On the basis of previous estimates, we calculated that comparison of intravenous immunoglobulin and methylprednisolone would require 130 patients in each treatment group (response rates; 52·5% *vs* 70%, with a type I error of 5% and a power of 80% in a two-tailed test), whereas the prednisone-placebo comparison would require 60 patients in each group (70% *vs* 42·5%, with a type I error of 5% and a power of 80% in a two-tailed test). Overall, 260 patients had to be recruited. We calculated sample size with Splus software, version 3.4 (MathSoft Inc, Seattle, WA, USA), based on a two-sided χ^2 test. With the calculated sample sizes we could detect at least a 2·8-day difference in mean number

of days with a platelet count above 50×10^9/L (assuming a SD of 8 days).

Statistical analysis

Data were analysed by intention to treat. Baseline comparisons between randomisation groups were based on Fisher's exact test and the non-parametric Wilcoxon's rank sum test. To analyse mean platelet counts and responder rates over time (from day 2 to day 5), a repeated-measure analysis of variance was used to assess the first randomisation effect. Regarding the other outcome measures, and owing to the 2×2 factorial design, we first looked at two potential interactions between the two randomisations with a generalised linear model (for continuous outcomes such as platelet counts and percentages after angular transformation), a logistic model (for binary outcomes), or a Cox's model (for censored outcomes). In the absence of interaction, the effect of each randomisation could be tested directly with these regression models by an F test or a likelihood ratio test.

We calculated the number of days (between day 1 and day 21) on which platelet counts exceeded either 20×10^9/L (and twice the baseline count) or 50×10^9/L after recoding missing data, assuming a linear relation between measurements. Linearity was also assumed when analysing platelet counts from day 21 to day 360. Platelet counts were not calculated when there was a treatment switch. We estimated failure time (switch and failure) with the Kaplan-Meier method.

The original design was a fixed-sample design based on standard hypothesis-testing considerations. An interim analysis was scheduled to be done after about 100 patients were enrolled, with attention to stopping rules. Results of the interim analysis were confined to evaluation of general monitoring of the trial (including analysis of serious adverse events) and of the main outcome measure. The statistical stopping rule relied on p values; all statistical tests were two-sided, with a type I error at 0·05. However, owing to the interim analyses, $p\leqslant0{\cdot}029$ defined statistical significance. We used SAS version 6.12 (Cary, NC, USA) statistical software package.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients

The study-monitoring committee ended the study after 122 patients had been enrolled, because results of the interim analysis showed a significant difference in the primary outcome measure between treatment groups. The study was stopped at 48 months.

Six patients were excluded from the analysis for the following reasons: HIV infection (n=2); lympho-proliferative disease (2); aplastic anaemia (1); and hyperthyroidism (1). Thus, 116 patients were assessable. 56 patients were assigned intravenous immunoglobulin, and 60 were assigned high-dose methylprednisolone (randomisation A). 62 were subsequently assigned placebo and 54 prednisone (randomisation B; figure 1). Baseline characteristics of patients in the two randomisations (in particular, platelet counts and haemorrhagic scores) were closely similar between the four groups (table 1).

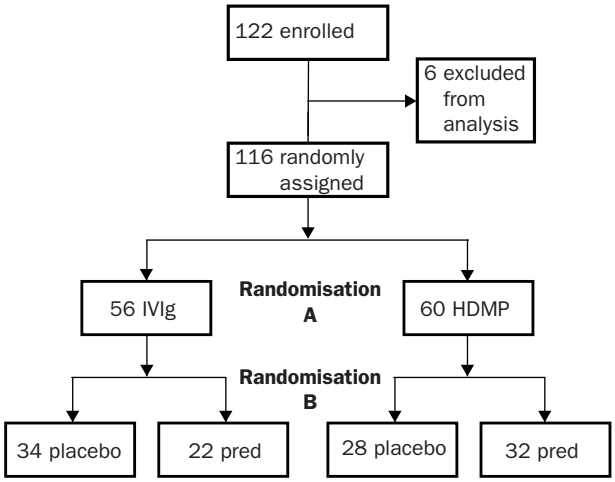


Figure 1: **Trial profile**
IVIg=intravenous immunoglobulin; HDMP=high-dose methylprednisolone; pred=prednisone.

Overall response

Table 2 shows results for short-term and long-term outcomes, according to the four groups obtained by simultaneous double randomisation. There was no evidence of interaction between the two randomisations for any outcome measures, so main randomisation effects could be directly analysed for short-term and long-term outcomes.

Short-term outcomes

The median number of days with platelet counts greater than 50×10^9/L and greater than 20×10^9/L were significantly higher in patients assigned intravenous immunoglobulin at randomisation A than in those assigned high-dose methylprednisolone (table 3). Likewise, median platelet counts between day 2 and day 5 (before randomisation B) were significantly higher in patients in the intravenous immunoglobulin group than in those in the high-dose methylprednisolone group (table 4). The proportion of patients who had platelet counts greater than 50×10^9/L during the same period was also significantly higher in the intravenous immunoglobulin group than in the high-dose methylprednisolone group (p=0·04), as was the

	Total (n=116)	IVIg-placebo (n=34)	HDMP-placebo (n=28)	IVIg-pred (n=22)	HDMP-pred (n=32)
Baseline characteristics					
Male sex	39 (34%)	12 (35%)	12 (43%)	7 (32%)	8 (25%)
Age (years)	38 (24–59)	39 (26–55)	45 (26–61)	41 (27–59)	30 (22–56)
Platelet count ($\times10^9$/L)	7 (3–12)	6 (2–9)	8·5 (3–13)	9 (5–13)	7·5 (2–12)
Platelet count <10×10^9/L	73 (63%)	26 (76%)	15 (54%)	11 (50%)	21 (66%)
Haemorrhagic score on day 1	4 (1–8)	4 (1–7)	2·5 (1–6)	5·5 (1·5–9)	4 (1–7·5)

HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin; pred=prednisone. Data are median (IQR) for continuous variables and number of patients (%) for discrete variables.

Table 1: **Main characteristics of patients at baseline, according to randomisation**

	IVIg-placebo (n=34)	HDMP-placebo (n=28)	IVIg-pred (n=22)	HDMP-pred (n=32)	p for interaction*	p for subset comparison†
Short-term response						
Platelet count (number of days)						
>50×10⁹/L	14 (2–19)	5 (0·5–15)	18·5 (18–19)	17·5 (12–18·5)	0·96	0·005
>20×10⁹/L and two-fold baseline value	18 (6–19)	8 (2–17)	19 (19–20)	19 (15–19)	0·82	0·008
HIghest platelet count after treatment						
⩽20×10⁹/L or <two-fold baseline value	6 (18%)	5 (18%)	0	2 (6%)	0·69	0·19
21–50×10⁹/L	2 (6%)	2 (7%)	0	4 (12%)		
51–150×10⁹/L	8 (23%)	15 (54%)	4 (18%)	6 (19%)		
>150×10⁹/L	18 (53%)	6 (21%)	18 (82%)	20 (63%)		
Response on day 21‡						
⩽20×10⁹/L or <two-fold baseline value	15 (44%)	17 (61%)	1 (5%)	5 (16%)	0·89	0·52
21–50×10⁹/L	4 (12%)	2 (7%)	1 (5%)	3 (9%)		
51–150×10⁹/L	7 (21%)	6 (21%)	7 (32%)	9 (28%)		
>150×10⁹/L	8 (23%)	3 (11%)	13 (59%)	15 (47%)		
Number of treatment switches	15 (44%)	16 (57%)	1 (5%)	6 (19%)	0·35	0·22
Long-term response						
Response at month 12‡						
Failure	24 (71%)	19 (68%)	12 (55%)	17 (53%)	0·90	0·36
51–150×10⁹/L	1 (3%)	1 (4%)	3 (14%)	1 (3%)		
>150×10⁹/L	9 (26%)	8 (28%)	7 (32%)	14 (44%)		
Median time to failure§ (days)	41·5 (20–126)	13 (10–NA)	120 (58–NA)	287·5 (50–NA)	0·89	0·12

HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin; pred=prednisone. NA=not available. Data are median (IQR) for continuous variables and number of patients (%) for discrete variables (unless otherwise stated). *Test for interaction between the two randomisation procedures, based on generalised linear modelling with F-test logistic model or Cox's model with likehood ratio test. †Comparison of outcome between IVIg-pred and HDMP-pred (ie, effect of randomisation A in the subset of patients who received pred after randomisation B), based on non-parametric Wilcoxon's rank sum test or Fisher's exact test. ‡Platelet count. §Estimated by the Kaplan-Meier method (95% CI).

Table 2: **Short-term and long-term outcomes**

proportion of patients who had platelet count greater than 20×10⁹/L and two-fold the baseline value (p=0·06). By contrast, overall distribution of highest platelet count between day 1 and day 21 (table 3), number of patients who were switched to another treatment (figure 2), and distribution of platelet count on day 21 (table 3) were not significantly different between the two groups of patients.

The median number of days with a platelet count greater than 50×10⁹/L and greater than 20×10⁹/L was significantly higher in patients assigned prednisone at randomisation B than in those assigned placebo (table 3). Prednisone was also associated with a larger number of responders on day 21, a higher platelet count between day 1 and day 21 (table 3), and a smaller number of switches to other treatments during the first 21 days after enrolment (figure 2) than placebo.

Since prednisone was more effective than placebo for all outcome measures, and because intravenous immunoglobulin was more effective than high-dose methylprednisolone for the primary outcome and several secondary outcomes, we compared patients treated with intravenous immunoglobulin plus prednisone with those treated with high-dose methylprednisolone plus prednisone (table 2). Patients who received intravenous immunoglobulin and prednisone had significantly more days with a platelet count greater than 50×10⁹/L and greater than 20×10⁹/L between day 1 and day 21 than those treated with high-dose methylprednisolone and prednisone (table 2). All patients who received intravenous immunoglobulin plus prednisone were classified as responders (ie, platelet count above 50×10⁹/L) compared with over four-fifths of those who received high-dose methylprednisolone plus prednisone (p=0·07). No difference between the two treatments was seen in terms of the other outcome measures.

Long-term responses

Of the 116 enrolled patients, 65 (56%) patients were followed up for 12 months, 43 (37%) were followed up for 9–12 months, five were followed up for 6–9 months, and three (3%) were lost to follow-up after 3–6 months. No patients died or had life-threatening haemorrhagic events. 72 patients were not in remission after initial treatment (failure, n=45; relapse after transient

	Randomisation A			Randomisation B		
	IVIg (n=56)	HDMP (n=60)	p*	Placebo (n=62)	Pred (n=54)	p*
Number of days with platelet count						
>50×10⁹/L	18 (7·5–19)	14 (2–18)	0·02	7 (1–18)	18 (15–19)	0·0001
>20×10⁹/L and two-fold baseline value	19 (12·5–20)	17 (6–19)	0·03	13·5 (4–19)	19 (18–19)	0·0001
Highest platelet count after treatment						
⩽20×10⁹/L or <two-fold baseline value	6 (11%)	7 (12%)	0·09	11 (18%)	2 (4%)	0·01
21–50×10⁹/L	2 (4%)	6 (10%)		4 (6%)	4 (7%)	
51–150×10⁹/L	12 (21%)	21 (35%)		23 (37%)	10 (19%)	
>150×10⁹/L	36 (64%)	26 (43%)		24 (37%)	38 (70%)	
Platelet count day 21						
⩽20×10⁹/L or <two-fold baseline value	16 (29%)	22 (37%)	0·15	32 (52%)	6 (11%)	0·0005
21–50×10⁹/L	5 (9%)	5 (8%)		6 (10%)	4 (7%)	
51–150×10⁹/L	14 (25%)	15 (25%)		13 (21%)	16 (30%)	
>150×10⁹/L	21 (38%)	18 (30%)		11 (18%)	28 (52%)	

HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin; Pred=prednisone. Data are median (IQR) for continuous variables and number of patients (%) for discrete variables. *Based on F test, with generalised linear model incorporating both treatment effects and interaction term between randomisations.

Table 3: **Short-term outcomes according to randomisation (A and B)**

	IVIg (n=56)	HDMP (n=60)	p*
Platelet count ($\times10^9$/L)			
Day 2	15·5 (7–25)	13 (3·5–25)	0·006
Day 3	40·5 (21–69·5)	34·5 (8·5–62·5)	
Day 4	84·5 (52–125)	61 (16–99)	
Day 5	122·5 (62·5–175·5)	79·5 (31–116)	
Platelet count >20$\times10^9$/L and two-fold baseline value			
Day 2	17 (30%)	11 (18%)	0·06
Day 3	42 (75%)	37 (62%)	
Day 4	47 (84%)	44 (73%)	
Day 5	50 (89%)	48 (80%)	
Platelet count >50$\times10^9$/L			
Day 2	4 (7%)	1 (2%)	0·04
Day 3	23 (41%)	20 (33%)	
Day 4	43 (76%)	36 (60%)	
Day 5	44 (79%)	36 (60%)	

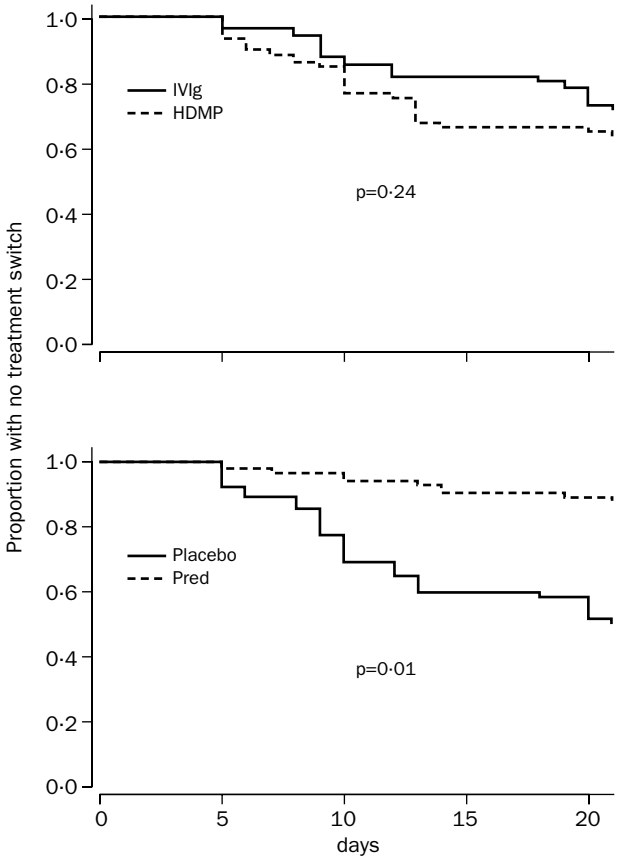
HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin. Data are median (IQR) or number of responders (%). *Based on F test by repeated measures analysis of variance that incorporated interaction between time and treatment effect on mean platelet count or on percentage of responders (after angular transformation).

Table 4: **Response between day 2 and day 5 according to randomisation A**

response, 27). Of the 51 patients who were followed up for less than 1 year, only four were responders at the last assessment (6, 6, 11, and 11 months after inclusion). The percentage of remissions was closely similar between the four groups of patients (p=0·58) and between randomisation groups A and B (table 5). Median time to relapse after treatment was significantly longer in patients receiving prednisone than in those given placebo (table 5). During 12-month follow-up, 22 (19%) patients underwent splenectomy: (five in the intravenous immunoglobulin-placebo group; three in the intravenous immunoglobulin-prednisone group; nine in the high-dose methylprednisolone-placebo group; and five in the high-dose methylprednisolone-prednisone group).

Adverse effects

Transient adverse effects were seen in 28 patients (24%). The frequency of adverse effects was the same in the four groups of patients (data not shown), and all patients made a full recovery. 14 (25%) patients receiving intravenous immunoglobulin had adverse effects, mainly headache (n=6) and fever (5). Headache was associated with a single episode of convulsions in one patient. Another patient had deep venous thrombosis complicated by pulmonary embolism. Adverse effects related to intravenous immunoglobulin infusion lengthened hospital stay for four patients. 14 (23%) patients receiving high-dose methylprednisolone had adverse effects, including diabetes mellitus (5) and arterial hypertension (2), and treatment had to be stopped for two patients. Adverse effects related to high-dose methylprednisolone infusion did not lengthen hospital stay.



Number of exposed patients

Randomisation A					
IVIg	56	56	49	46	44
HDMP	60	60	51	40	40
Randomisation B					
Placebo	62	62	48	37	36
Pred	54	54	52	49	48

Figure 2: **Time to treatment switch after enrolment according to randomisation A (top) and randomisation B (bottom)**
HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin; Pred=prednisone. Non-parametric Kaplan-Meier estimates were calculated, with p based on likelihood ratio test on the basis of Cox's model incorporating both randomisation effects and interaction term.

Discussion

Our data lend support to use of intravenous immunoglobulin plus oral prednisone as first-line treatment for patients with severe AITP, because this treatment induces more sustained and rapid short-term responses than other treatments. However, high-dose methylprednisolone plus oral prednisone was also well tolerated and effective. Moreover, no difference in long-term response was seen whatever the treatment. Thus, in

	Randomisation A			Randomisation B		
	IVIg (n=56)	HDMP (n=60)	p	Placebo (n=62)	Pred (n=54)	p
Response at month 12*						
Failure	36 (64%)	36 (60%)	0·80	43 (69%)	29 (54%)	0·41
51–150$\times10^9$/L	4 (7%)	2 (3%)		2 (3%)	4 (7%)	
>150$\times10^9$/L	16 (29%)	22 (37%)		17 (27%)	21 (39%)	
Time to failure† (days)	69·5 (32–134)	110 (23–NA)	0·24	22·5 (13–96)	152 (90–NA)	0·01

HDMP=high-dose methylprednisolone; IVIg=intravenous immunoglobulin; Pred=prednisone; NA=not available. Data are number (%) for discrete variables amd median (95% CI) for censored variables. *Platelet count. †Failure was defined as any treatment change whatever the date or as a platelet count ⩽50$\times10^9$/L between day 21 and month 12. Median time to failure was estimated by the Kaplan-Meier method, with 95% CI calculated from the 95% bounds of the Kaplan-Meier curve obtained by applying the Greenwood formula of variance. p values were calculated by regression models (either generalised linear model after arc sinus transformation or Cox's model) incorporating randomisation A and B effects and interaction term.

Table 5: **Long-term outcomes according to randomisation**

our opinion, only patients with the most severe forms of AITP should receive intravenous immunoglobulin and prednisone.

Treatment of AITP is poorly standardised, and as presented in textbooks and reviews, it is not based on clinical trial data but on compilations of uncontrolled case series.[20] However, there is international agreement on the need to offer an active treatment to patients who have symptoms, have a platelet count below 10×10^9/L, or both.[2,21] Most patients enrolled in our study met these criteria. Clinical trials in AITP should ideally focus on the effect of treatment on risk of severe bleeding or death, but these events are very rare.[22] Thus, with these outcomes, we would need to enrol more than 1000 patients to show a clinical benefit, which is not feasible. On the other hand, investigators have shown that patients with very low platelet counts ($<10\times10^9$/L) are at risk of severe bleeding.[2,21,23] We thus chose platelet count as the primary outcome measure to assess response to treatment, because it is a relevant and simple surrogate marker.

Our first aim was to assess response to a 3-day course of either intravenous immunoglobulin or high-dose methylprednisolone in previously untreated adults with severe AITP. We compared intravenous immunoglobulin with high-dose methylprednisolone rather than oral prednisone because results of several studies have suggested that high-dose methylprednisolone might be a more effective first-line treatment than oral corticosteroids in terms of response rate and time needed to respond.[14–17] Moreover, some patients who are resistant to oral prednisone respond to high-dose methylprednisolone.[16,18] Intravenous immunoglobulin was more effective than high-dose methylprednisolone, because the number of days with a platelet count higher than 50×10^9/L or 20×10^9/L between days 1 and 21 after beginning treatment was significantly higher in patients receiving intravenous immunoglobulin. Response was also more rapid with intravenous immunoglobulin than high-dose methylprednisolone, because more patients receiving the former had platelet counts above a safe haemostatic level ($>50\times10^9$/L) within the first 5 days.

Our second aim was to assess use of oral prednisone (1 mg per kg bodyweight per day for 18 days, then rapid tapering) after high-dose methylprednisolone or intravenous immunoglobulin infusion. Oral prednisone was beneficial: relative to the placebo group, patients receiving prednisone had significantly more days with a protective platelet count between days 1 and 21, and they were also more likely to be in remission on day 21 and less likely to switch to another treatment between day 1 and day 21. Moreover, patients who received oral prednisone relapsed less rapidly than patients who received placebo (table 5). The significantly better treatment response in patients receiving intravenous immunoglobulin and oral prednisone than in those receiving high-dose methylprednisolone and oral prednisone is another important finding. This benefit affected the primary outcome measure (ie, number of days with a safe platelet count between day 1 and day 21). All patients treated with intravenous immunoglobulin and prednisone had a platelet count greater than 50×10^9/L, compared with only 82% of those treated with high-dose methylprednisolone and prednisone (p=0·07). Moreover, the trend towards a lower rate of treatment switches among the patients treated with intravenous immunoglobulin plus prednisone suggests a clinical advantage relative to high-dose methylprednisolone plus prednisone.

A subsidiary aim of our study was to compare the effect of first-line treatment on the later outcome of disease. There is little evidence in published work that first-line treatment affects the progression of AITP to chronicity.[24] Because we did not include a control group of untreated patients, we cannot fully assess this aim. However, the remission rate at 1 year did not differ by treatment initially received, and was similar to published values.[1] The 18-day course of prednisone did not prevent progression to chronicity (relative to placebo), which is noteworthy. These results strongly suggest that intravenous immunoglobulin, steroids, or both do not modify the natural history of severe AITP in adults, and support the assumption that prednisone has only a delaying action in this setting.

Contributors

P Bierling, B Godeau, B Varet, J-M Zini, C Chastang, and F Bassompierre had the original idea for the protocol. B Godeau, P Bierling, and S Chevret wrote and revised the paper. S Chevret did the statistical analyses. B Godeau, F Lefrère, J-M Zini, S Chèze, E Legouffe, C Hulin, M-J Grange, O Fain, P Bierling, and B Varet were responsible for inclusion of patients.

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Conflict of interest statement

None declared.

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