

Initial Management of Immune Thrombocytopenic Purpura in Adults: A Randomized Controlled Trial Comparing Intermittent Anti-D With Routine Care

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We conducted a randomized clinical trial in adults with a new diagnosis of ITP and a platelet count $<30,000/\mu\text{L}$ to test the hypothesis that initial intermittent treatment with anti-D may avoid or defer the need for splenectomy when compared to current routine care (glucocorticoid treatment, followed by splenectomy). Splenectomy was to be performed in the anti-D group if patients failed to respond to three consecutive anti-D treatments given within 10 days. The incidences of splenectomy were 14 of 37 (38%) in the routine care group and 14 of 33 (42%) in the anti-D group (absolute risk reduction = 4.6% in favor of the routine care group, 95% CI, -18.4 to 27.6%). However, splenectomy was performed prematurely, not according to the protocol, in 11 of 14 patients in the anti-D group. The median time to splenectomy was 36 days (range, 9–78) in the routine care group and 112 days (range, 19–558) in the anti-D group ($P = 0.045$ at 100 days after randomization, $P = 0.840$ at 1 year after randomization, using log-rank analysis). Patients in the anti-D group were treated with prednisone for fewer days (70 days) compared to the routine care group (112 days, $P = 0.01$). No major bleeding events occurred. In this study, initial treatment of patients with intermittent anti-D initially deferred splenectomy. Whether our aggressive regimen of anti-D could have prevented splenectomy if it had been adhered to in all patients remains uncertain. However, compliance with this anti-D regimen was not feasible for many patients and/or their physicians. *Am. J. Hematol.* 74:161–169, 2003. © 2003 Wiley-Liss, Inc.

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) in children often resolves spontaneously within 6 months. Therefore, routine care for children is generally short-term and is reserved for selected patients with severe thrombocytopenia and bleeding symptoms; splenectomy is rarely performed [1–3]. For children who do require therapy, anti-D immunoglobulin is the most frequently used agent for initial treatment in the United States [4]. Intermittent anti-D treatment has also been used in children with persistent thrombocytopenia to avoid side effects of glucocorticoids and to defer splenectomy [5].

In contrast, spontaneous remission of ITP in adult patients is considered to be rare [1,2]. The initial management of adults with ITP has not changed since the introduction of glucocorticoids over 50 years ago [1,2,6]. Initial treatment with glucocorticoids is routine care, usually resulting in a platelet count response but not a complete remission [1,2]. For patients with persistent and clinically important thrombocytopenia, splenectomy is routine care, usually performed 4–6 weeks after diagnosis [1]. This results in a sustained complete remission in approximately two-thirds of patients [1,2].

In an uncontrolled study of adults with ITP, Cooper et al. [7] reported that 8 of 28 (29%) patients treated with intermittent doses of anti-D underwent splenectomy, a result interpreted by the authors to indicate that intermittent anti-D treatment allowed more than 40% of patients to avoid splenectomy. If the use of intermittent anti-D safely allows deferral of splenectomy for longer than the usual practice of 4–6 weeks, this may provide time for previously unappreciated spontaneous remissions to occur. Deferral of splenectomy would be especially important for older patients, who are being diagnosed with ITP with increasing frequency [8] and who may have more co-morbid conditions. Intermittent anti-D treatment may also diminish the use of glucocorticoids which may decrease the risk for critical infections [9,10].

We report the results of a randomized clinical trial in adults with a new diagnosis of severe ITP that compared intermittent anti-D treatment to routine care consisting of prednisone followed by splenectomy. The outcome measures were 1) time to or the need for splenectomy (effectiveness), and 2) incidence of new episodes of major bleeding (safety). The primary hypotheses were that anti-D therapy would delay the need for splenectomy and that the incidence of new major bleeding would be low and similar in the two groups.

PATIENTS AND METHODS

Patients

The study population consisted of consecutive adult patients with acute ITP referred to one of the participating hematologists. Inclusion criteria were: 1) age ≥ 18 years; 2) a new diagnosis of ITP [1] within the past 30 days with a platelet count $< 30,000/\mu\text{L}$; and 3) Rh_o (D) positive. Patients were ineligible if they had one or more of the following: 1) history of anaphylaxis to plasma products; 2) hemoglobin < 8 g/dL; 3) history of splenectomy; 4) pregnant or nursing women; 5) prior treatment with anti-D; 6) received investigational agents within 30 days prior to enrollment; 7) history of IgA deficiency, defined as < 5 mg/dL; and 8) failure or inability to provide informed consent. Treatment with other noninvestigational therapies such as glucocorticoids prior to enrollment was allowed.

Patients were stratified according to the participating center and by age (< 50 years, ≥ 50 years) and then randomly allocated to be managed by routine care or to receive anti-D. Within each stratum the randomization was computer-generated and balanced by blocking. Patients were to be followed until 12 months after the enrollment of the last patient.

The protocol was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center and by the Institutional Review Boards at each of the participating sites. The study was monitored by an independent Data Safety Monitoring Board.

Treatment Regimens

Routine care. Patients randomized to management according to routine care were treated with prednisone, 1 mg/kg/day as a single dose, for 14 days from the time of randomization. This regimen was used to ensure that all patients received an adequate course of prednisone therapy. After 14 days, the further use of prednisone was at the discretion of the patient's physician. During the initial 14 days the criterion for splenectomy was a new occurrence of major bleeding. If the platelet count was persistently $< 30,000/\mu\text{L}$ during the first 14 days of treatment, splenectomy was to be performed when clinically feasible but within the next 4 weeks [1]. If the platelet count was $> 30,000/\mu\text{L}$ 14 days after randomization or increased to $> 30,000/\mu\text{L}$ prior to splenectomy, the patient was to be treated with prednisone and/or splenectomy at the discretion of the physician. These criteria were developed to reflect routine practice. The criteria were clearly defined for the first 14 days after randomization; however, there is no

consensus on indications for prednisone or splenectomy after 14 days [1]. Therefore, splenectomy was allowed according to the physician's judgment so the results of the routine care group would be generalizable to clinical practice.

All other treatments for ITP, including anti-D, were prohibited until the patient had a new major bleeding event or had undergone splenectomy. Platelet transfusions for patients with major bleeding were allowed at the discretion of the patient's physician. The criteria for treatment with intravenous immune globulin (IVIG) were: 1) a new major bleeding event; 2) overt bleeding which did not meet criteria for major bleeding in a patient with a platelet count $< 10,000/\mu\text{L}$; or 3) to prepare the patient for splenectomy or other surgical procedure. The IVIG regimen was at the discretion of the patient's physician.

Anti-D. Patients randomized to the anti-D group received concomitant prednisone and anti-D. Prednisone, 1 mg/kg/day as a single dose, was administered for 14 days from the time of randomization and then tapered every 3 days by one-half the previous dose until reaching a dose of 5 mg/day for 3 days and then discontinued. All patients received anti-D intravenously immediately following randomization regardless of the platelet count. The initial and subsequent doses of anti-D were given according to the algorithm in Table I. Splenectomy was to be performed for either 1) a new major bleeding event; 2) failure of the initial three consecutive treatments with anti-D to increase the platelet count to $> 30,000/\mu\text{L}$; 3) relapse of thrombocytopenia ($< 30,000/\mu\text{L}$) and failure of three additional treatments with anti-D to increase the platelet count to $> 30,000/\mu\text{L}$; or 4) inability to give anti-D for two consecutive treatments because the hemoglobin remained < 8.0 g/dL. Continued treatment with prednisone was allowed for patients with platelet counts $< 30,000/\mu\text{L}$. All other treatments for ITP were prohibited until the patient had a new major bleeding event or had undergone splenectomy. The use of platelet transfusions and IVIG was allowed according to the criteria specified for the routine care group.

Outcome Measures

The primary outcome of effectiveness was the time until splenectomy. Secondary outcomes included 1) the proportion of patients in whom splenectomy was avoided, and 2) complete and partial remissions. A complete remission was defined as a normal platelet count without treatment for > 3 months and without subsequent relapse. A partial remission was defined as a platelet count $> 30,000/\mu\text{L}$ but less than normal without treatment for > 3 months and without relapse. Patients who were not followed to document platelet counts for > 3 months, who required continued treatment, or who had platelet counts $< 30,000/\text{mL}$ were considered to have had no response. We also measured and compared the number of days on prednisone therapy to determine if treatment with anti-D resulted in fewer days of steroid use.

The primary outcome of safety was the incidence of new episodes of major bleeding occurring after randomization. Major bleeding was defined as clinically overt bleeding associated with either a decrease in hemoglobin of ≥ 2 g/dL or the requirement for transfusion of ≥ 2 units of red blood cells; or bleeding that was intracranial, intraocular, retroperitoneal, or intra-articular in a major joint. These criteria have been shown to be reproducible and valid indices of clinically relevant bleeding in clinical trials of anticoagulation therapy [11]. Secondary outcomes of safety included: 1) minor bleeding, defined as overt bleeding which did not meet the criteria for major bleeding, and 2) death from any cause. Adverse effects of treatment were also documented.

Statistical Analysis

It was estimated from the literature that fewer than 20% of adult patients with severe ITP, defined as an initial platelet count $< 30,000/\mu\text{L}$, would achieve a complete remission with glucocorticoids [1] and that the patients without complete remissions would require splenectomy. For sample size calculation the following assumptions were made: 1) true cumulative

TABLE I. Anti-D Treatment Algorithm

Plt ($10^3/\mu\text{L}$)	Hb (g/dL)	Anti-D ($\mu\text{g}/\text{kg}$)	Additional Action
≤ 30	≥ 10.0	75	Repeat Hb and platelet ct in 4 days; reevaluate
≤ 30	8.0 to 10.0	50	Repeat Hb and platelet ct in 4 days; reevaluate
≤ 30	< 8.0	None	Repeat Hb and platelet ct in 4 days; reevaluate
> 30	Not applicable	None	Repeat Hb and platelet ct at scheduled visit; reevaluate

If the hemoglobin (Hb) was > 8.0 gm/dL, anti-D was not withheld unless the change in hemoglobin was ≥ 3.0 gm/dL, or a lesser degree of hemolysis resulted in clinically important manifestations in the judgment of the treating physician.

splenectomy rates at 1 year are 80% in the control group and 60% in the anti-D group; 2) patient accrual will take 2.5 years; 3) patients will be followed for 1 year after the last patient is enrolled; 4) the loss to follow-up rate for each treatment group will be 10% per year; 5) two-sided alpha of 0.05. Based on these assumptions and using the methodology of Lachin and Foulkes [12], 35 patients per treatment group will provide 91% power to detect a significant difference between treatment groups.

Intention-to-treat analyses were used except where specified. Kaplan-Meier analysis and the log-rank test were used for the time-to-occurrence of splenectomy. Patients were censored at the last day of their follow-up if they had not reached the primary effectiveness outcome of splenectomy. The proportions between groups of patients having splenectomy, or achieving complete, partial, or no remission were compared by chi-square or Fisher's exact test where appropriate. The number of days of prednisone use between the two treatment groups was assessed by the Wilcoxon test. Baseline characteristics were compared using appropriate statistical tests, including the *t*-test, Wilcoxon test, chi-square, and/or Fisher's exact test.

RESULTS

Patient Enrollment

Twenty study sites in the United States enrolled between 1 and 10 patients each (median, 2.5 patients) between November 26, 1997, and July 5, 2000. Of the

70 patients enrolled, 37 were randomized to the routine care group and 33 to intermittent anti-D treatment.

Patient Characteristics and Follow-up

Table II describes the presenting clinical features and duration of follow-up. Three patients were found to be ineligible after randomization. In the routine care group, one patient was Rh₀ (D)-negative. In the anti-D group, the diagnosis of one patient was changed to aplastic anemia 3 days after randomization. Another patient in the anti-D group had been on an investigational agent for prostate cancer prevention within 30 days of enrollment. These patients were included in the intention-to-treat analysis.

Median follow-up durations were similar for the two groups (anti-D 505 days, routine care 424 days, *P* = 0.301). Thirty-five patients (50%) completed at least 1 year of follow-up, and 23 additional patients (33%) completed at least 6 months of follow-up. Follow-up was terminated earlier than 6 months for 12 patients: eight patients who withdrew from the study or failed to keep appointments, two patients who had violated enrollment criteria, one patient who died 73 days after enrollment, and one patient who moved out of the country.

Protocol violations. Five of the 37 patients in the routine care group had protocol violations: one patient had a splenectomy performed 9 days after randomization, one patient received anti-D, one patient received a platelet transfusion, and one other patient received both a platelet transfusion and IVIG not according to

TABLE II. Patient characteristics and follow-up

	Routine care (n = 37)	Anti-D (n = 33)	<i>P</i> value
Age			
Mean ± SD	50 ± 17	43 ± 19	0.08
No. > 60 yrs (%)	12 (32)	6 (18)	
Female (%)	24 (65)	22 (67)	0.87
Platelet count ^a			
< 10,000/μL (% subj.)	12 (32)	18 (55)	0.06
< 20,000/μL (% subj.)	23 (62)	27 (82)	0.07
Follow-up (days)			
Mean (range)	424 (28–1,175)	505 (3–1,120)	
median	361	421	0.30
Other therapies ^b			
Platelets	3	4	
IVIg	5	5	
Danazol, platelets	0	1	
Danazol & vincristine	1	0	
Danazol, AZ, IVIg	1	0	
CP, IVIg	0	1	

^aPlatelet counts are lower of two values (initial screening visit and day of randomization).

^bAdditional therapy during the study; 8 of 21 patients received regimens in violation of the protocol (five in the routine care group, three in the anti-D group).

IVIg = nonspecific immunoglobulin; AZ = azathioprine; CP = cyclophosphamide.

protocol, and one patient received vincristine and danazol without having a splenectomy (Table II).

Fifteen of 33 patients in the anti-D group had protocol violations. In 11 of the 14 patients who had a splenectomy, it was not performed according to the protocol that required failure to respond to three consecutive anti-D treatments given within 10 days. Most of these patients had multiple but brief responses to anti-D and the decision for splenectomy was made by the patient and physician as a preference to continued anti-D treatments. Three additional patients who did not have a splenectomy did not follow the anti-D treatment algorithm (Table I); one patient received a platelet transfusion not according to protocol.

Anti-D Dose Adjustments

Twenty-five of 32 patients (78%) received the maximum dose of 75 $\mu\text{g}/\text{kg}$ of anti-D for each of their treatments. Seven patients required an anti-D dose adjustment according to the protocol (Table I): two had a hemoglobin less than 10 g/dL at the time of their initial treatment, three had a hemoglobin decrease of > 3 g/dL following anti-D administration, two additional patients decreased their hemoglobin to < 10 g/dL.

Effectiveness Outcomes

Time to splenectomy. *Intention-to-treat analysis.* Among the 14 patients in the routine care group

who had splenectomy, the median time to splenectomy was 36 days (mean, 37 days; range 9–78 days); among the 14 patients in the anti-D group who had splenectomy, the median time to splenectomy was 112 days (mean, 148 days; range 19–558 days). Figure 1 demonstrates the Kaplan-Meier curves at 1 year; 27 of 28 splenectomies occurred during this time. The difference between the two groups at 1 year was not significant ($P = 0.840$, using a log-rank analysis). Because most splenectomies as part of routine care are performed within 100 days [1] and 19 of 28 splenectomies in this study were performed within 100 days, including all splenectomies in the routine care group, time to splenectomy was also compared between the two groups 100 days after randomization ($P = 0.045$, using a log-rank analysis).

Per-protocol analysis. Removing the 23 patients with eligibility or protocol violations, 3/16 (19%) of the patients in the anti-D group and 12/31 (39%) of the patients in the routine care group were splenectomized, and all occurred within 100 days of randomization ($P = 0.185$, log-rank test for difference in time to splenectomy).

Rates of splenectomy. The incidences of splenectomy were 14 of 37 (38%) in the routine care group and 14 of 33 (42%) in the anti-D group (absolute risk reduction = 4.6% in favor of the routine care group, 95% CI -18.4 to 27.6%) (Table III). The mean platelet counts prior to splenectomy were 17,000/ μL (range,

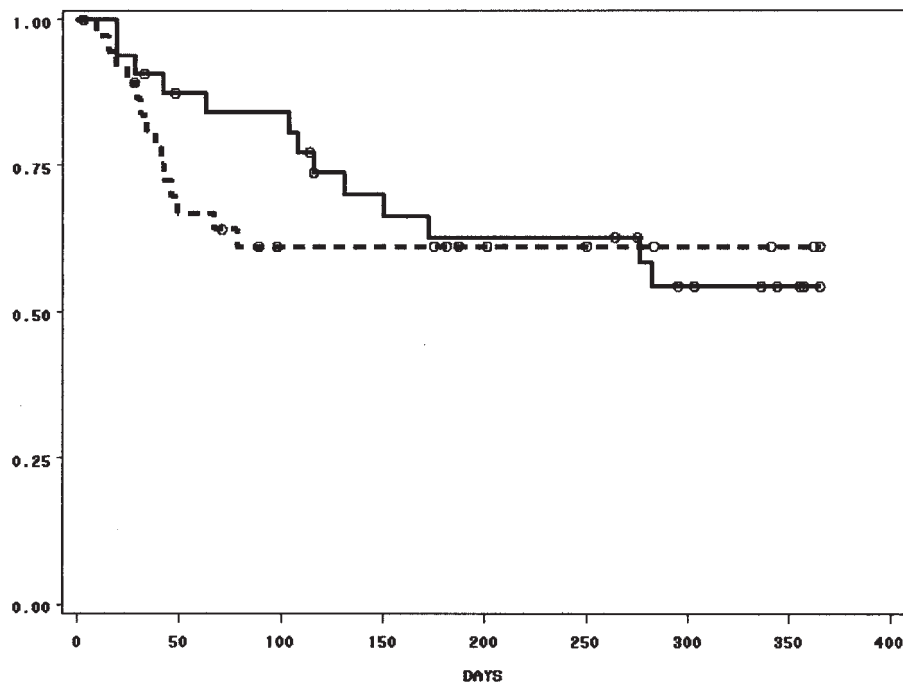


Fig. 1. Kaplan-Meier curves for time to splenectomy. These curves represent the time to splenectomy for the first year of follow-up for the patients treated with intermittent anti-D (solid line) or routine care (broken line). Circles indicate censored patients. Twenty-seven of 28 splenectomies occurred during this time. Log-rank analysis, $P = 0.840$.

2,000–33,000/ μL) in the routine care group and 11,000/ μL (range, 1,000–29,000/ μL) in the anti-D group. There was a trend toward a declining incidence of splenectomy rate in the routine care group during the course of the study (10 of 19 (53%) patients who were enrolled in 1997–1998 vs. 4 of 18 (22%) patients who were enrolled in 1999–2000, $P = 0.06$). The median follow-up durations for the patients enrolled in these two time periods were similar: 1997–1998, 348 days; 1999–2000, 369 days.

Remissions. The incidences of complete remission were 17 of 37 (46%) in the routine care group and 16 of 33 (49%) in the anti-D group (absolute risk reduction = -2.5% in favor of the anti-D group, 95% CI, -21.9 to 26.0%) (Table III). An additional 17 patients (12 in the routine care group and five in the anti-D group) had a normal platelet count at their last follow-up visit but did not meet the criteria of complete remission due to inadequate follow-up or continued therapy.

Response to anti-D. Thirteen patients had only one anti-D treatment, 19 patients had 2–10 anti-D treatments, and one patient (who was diagnosed with aplastic anemia after enrollment) did not receive anti-D treatment.

Among the 13 patients who had only one infusion of anti-D, 10 had a platelet count $> 30,000/\mu\text{L}$ at the time of the initial infusion, perhaps due to pre-enrollment prednisone treatment. Among the three patients with an initial platelet count $< 30,000/\mu\text{L}$, all increased their platelet count to $> 30,000/\mu\text{L}$ following anti-D administration. One of these 13 patients had a splenectomy and achieved a complete remission and 9 of the 12 patients who did not have a splenectomy also achieved a complete remission.

Among the 19 patients who received between 2 and 10 anti-D infusions, 15 (79%) responded with an increase in platelet count with $> 30,000/\mu\text{L}$ to at least one infusion. The platelet count increased to

TABLE III. Patient outcomes of effectiveness and safety

	Routine care (n = 37)	Anti-D (n = 33)	<i>P</i> value
Splenectomy (%)	14/37 (38)	14/33 (42)	
Time to splenectomy (days)			
mean (range)	37 (9–78)	148 (19–558)	
median	36	112	
Complete response ^a			
Splenectomized (%)	9/14 (64)	6/14 (43)	
Not splenectomized (%)	8/23 (35)	10/19 (53)	
All (%)	17/37 (46)	16/33 (49)	
Partial response ^a			
Splenectomized (%)	1/14 (7)	6/14 (43)	
Not splenectomized (%)	3/23 (13)	3/19 (16)	
All (%)	4/37 (11)	9/33 (27)	
No response ^a			
Splenectomized (%)	4/14 (29)	2/14 (14)	
Not splenectomized (%)	12/23 (52)	6/19 (32)	
All (%)	16/37 (43)	8/33 (24)	
Normal platelet count at last follow-up ^a			
Splenectomized (%)	14/14 (100)	9/14 (64)	
Not splenectomized (%)	15/23 (65)	12/19 (63)	
All (%)	29/37 (78)	21/33 (64)	
Days of prednisone ^b			
mean (range)	119 (20–1,110)	70 (3–407)	
median	64	32	0.01
Bleeding events			
Major	0	0	
Minor ^c	11	12	0.56
gastrointestinal	3	1	
menorrhagia	4	4	
hematuria	1	0	
oral/gingival	4	5	
epistaxis	6	7	
Deaths	1	1	

^aRemission status defined in Methods. Comparison of remission (complete, partial, none) between treatment groups, $P = 0.11$. Comparison of percent of patients with normal platelet counts between treatment groups, $P = 0.173$.

^bIncludes treatment with prednisone and other glucocorticoids (methylprednisolone, dexamethasone). The patient in the anti-D group who received only 3 days of prednisone was the patient whose diagnosis was changed to aplastic anemia.

^cSome patients had more than one minor bleeding event.

> 30,000/ μ L following 79% of the 73 infusions (median platelet count increment 64,000/ μ L, range 24,000/ μ L–326,000/ μ L). The median duration of response (days between infusion and platelet count < 30,000/ μ L) was 40 (range 4–450) days. Three (21%) patients did not respond to their initial three anti-D infusions; all were splenectomized, and one achieved a complete remission. One patient did not respond to two initial anti-D infusions and did not achieve a complete remission with splenectomy. Nine additional patients were splenectomized and four achieved a complete remission. Six patients were not splenectomized and one achieved a complete remission.

Days of prednisone treatment. Patients in the routine care group received significantly more days of prednisone (median 64 days, range 20–1, 110 days) than the anti-D group (median 32 days, range 3–407 days) ($P = 0.01$) (Table III).

Safety Outcomes

Major bleeding. No new episodes of major bleeding were observed in either treatment group throughout the course of the study.

Minor bleeding. In a total of 23 patients, 11 patients in the routine care group and 12 patients in the anti-D group had 35 new minor bleeding events. These included epistaxis, oral-gingival bleeding, menorrhagia, gastrointestinal bleeding, and hematuria (Table III).

Other adverse events. Seven of 32 patients (22%) had moderate or severe systemic symptoms following anti-D administration, including fever, chills, nausea, vomiting, and myalgias. Three patients had a hemoglobin decrease of ≥ 3 g/dL following anti-D administration; in one of these three patients, menorrhagia may have contributed to the hemoglobin decrease. Many patients in both groups described characteristic side effects of prednisone, such as moon face, weight gain, mood disorders, insomnia, weakness, and fatigue.

Deaths. Two patients died during the study. Both were unrelated to the study procedures or ITP. A 36-year-old woman in the routine care group died on day 73 with pulmonary hypertension, heart failure, and liver cirrhosis. At the time of death, her platelet count was 8,000/ μ L but at autopsy there was no hemorrhage or thrombosis. A 60-year-old woman in the anti-D group died on day 301, 95 days after splenectomy, with a platelet count of 419,000/ μ L. The cause of death was respiratory failure due to chronic obstructive pulmonary disease and chronic inflammatory demyelinating polyneuropathy.

DISCUSSION

This report describes the results of one of the few randomized clinical trials in adult ITP patients using

clinical outcomes. The objective was to determine if a novel strategy using intermittent treatment with anti-D for the initial management of adults with a new diagnosis of severe ITP would allow safe deferral and perhaps avoid the necessity for splenectomy. If splenectomy could be delayed, we postulated that previously unappreciated spontaneous remissions among adults might become apparent.

Although the anti-D group experienced an increase in time to splenectomy compared to the routine care group, we did not demonstrate a decreased rate of splenectomy. There appeared to be no increase in spontaneous remissions in the anti-D group. The overall splenectomy rate of 38% in the routine care group was only about half of our initial hypothesis that 80% of patients managed with routine care would require splenectomy by 1 year. This low rate of splenectomy occurred in spite of the severity of ITP among our patients. All patients had an initial platelet count < 30,000/ μ L; one-third had a platelet count < 10,000/ μ L at the time of screening or randomization. The low rate of splenectomy may reflect changing contemporary care. This is supported by the decreasing splenectomy rate over the course of our study involving 20 study sites. In a recent report of adult patients treated with intermittent anti-D, 29% of patients were splenectomized, an outcome that was interpreted to indicate that the anti-D treatment may have allowed 40% of patients to avoid splenectomy [7]. However splenectomy may not have been avoided in that study since it did not have a concurrent control group and the results of our trial suggest that current rates of splenectomy are much less than previously assumed.

In our randomized controlled clinical trial a difference in splenectomy rates between patients managed with intermittent anti-D or with routine care was not observed. These results are similar to a previous study of initial management of ITP in adults comparing patients receiving prednisone, intravenous immunoglobulin (IVIg), or both agents that demonstrated no difference between the groups in response rates, duration of response, or requirement for splenectomy [13]. However, in our clinical trial, because of the wide 95% confidence interval and the high rate of protocol violations, we cannot clearly establish or exclude our hypothesis that initial intermittent treatment with anti-D may prevent the need for splenectomy. Eleven of 14 patients in the anti-D group were splenectomized prematurely, not according to the protocol. If splenectomy had only been performed according to the protocol criteria, it is not possible to know how many patients would have ultimately required splenectomy and if intermittent anti-D treatment may have prevented the need for splenectomy in some patients.

Anti-D is approved for use at a dose of 50 µg/kg; our dose of 75 µg/kg was based on observations that this higher dose results in a greater frequency of responses without an increased risk of clinically important hemolysis [14]. Furthermore, our protocol required two subsequent doses at 4 ± 1-day intervals if the platelet count did not increase to > 30,000/µL. The criterion for splenectomy was failure of three consecutive doses of anti-D given within 10 days to increase the platelet count to > 30,000/µL (Table I). Therefore, the inability to avoid splenectomy by intermittent treatment with anti-D occurred in spite of our use of a regimen of anti-D that is more aggressive than the current standard regimen and that was designed to provide the maximum benefit from anti-D. However, the frequency of brief responses to anti-D made it difficult to meet the criterion for splenectomy of failure to respond to three consecutive treatments, and led to the frequent protocol violations, demonstrating that this aggressive regimen of anti-D was not feasible for many patients and/or their physicians.

Although a cost analysis was not done at the conclusion of this clinical trial, our protocol was used as the basis for a predictive cost analysis [15]. This analysis suggested that anti-D would be cost-effective if 47% or more patients in the anti-D group avoided splenectomy, compared to the routine care group. Therefore, our results suggest that, regarding prevention of splenectomy, anti-D may not be cost-effective.

The clinical outcomes of the two groups were similar, with 49% and 46% of patients in the anti-D and routine care groups, respectively, achieving a complete remission. The rates of remission were similar between the two groups for both splenectomized and nonsplenectomized patients. The frequency of patients defined as having no response was high because of the stringent definitions of complete and partial remission. Sixty-four percent of patients in the anti-D group and 78% of patients in the routine care group had a normal platelet count at the time of their last follow-up, and may have had a complete remission, but their follow-up was for less than 3 months or they were on continued steroid treatment.

The results of our study support the safety of these management approaches. No new episodes of major bleeding and no deaths from bleeding occurred, in spite of the severity of ITP in these patients. This is consistent with current impressions that major bleeding and mortality from ITP are low [9]. The occurrence of minor bleeding also was not different between the two treatment groups.

A limitation of this study was the difficulty in accruing patients with a new diagnosis of ITP, requiring over 2.5 years for 20 study sites to enroll 70 patients. The median number of patients enrolled by

each site was only 2.5, with six sites enrolling only one patient. This resulted in limited opportunity to gain experience with this complex protocol and made adherence to the protocol difficult. The involvement of many sites in this study also increased the potential for diversity of physician judgment; however, this diversity may reflect the range of community practices and enhance the generalizability of our results.

A further limitation was that our study was unblinded regarding therapy and the endpoint of splenectomy could have been influenced by the knowledge of the treatment group. This trial was specifically designed to compare anti-D to routine care; other treatment modalities may also allow a comparable deferral of splenectomy when compared to routine care.

In summary, these data support the safety of initial treatment with intermittent anti-D. Anti-D can diminish the use of prednisone and may defer, but may not prevent, splenectomy. Although ITP is typically considered to be a disorder of younger patients, 26% of our patients were over 60 years old, consistent with recent data describing an increasing frequency of ITP in older persons [8]. Deferral of splenectomy and diminished requirement for prednisone may be especially important for older patients. Older patients may have more comorbid conditions requiring delay of a surgical procedure and may have increased risks for the side effects of prednisone [9].

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APPENDIX

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