Twice-daily plasma exchange for patients with refractory thrombotic thrombocytopenic purpura: the experience of the Oklahoma Registry, 1989 through 2006

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BACKGROUND: Twice-daily plasma exchange has been used for patients with thrombotic thrombocytopenic purpura (TTP) who are unresponsive to treatment with daily plasma exchange for many years but with no clear evidence of effectiveness.

STUDY DESIGN AND METHODS: The 18 years' experience of The Oklahoma TTP-HUS (hemolytic-uremic syndrome) Registry, 1989 through 2006, with twice-daily plasma exchange for 31 episodes of TTP in 28 patients is reported. A definite response to twice-daily plasma exchange was defined a priori as a platelet (PLT) count increase after twice-daily plasma exchange on two separate occasions during the treatment of a single episode of TTP, with no change of other treatments. A possible response was defined as a PLT count increase after initiation of twice-daily plasma exchange only once with or without change of other treatments.

RESULTS: A definite response to twice-daily plasma exchange occurred in 3 episodes (three patients), 27 episodes had a possible response, and 1 episode had no response. The three patients with a definite response had ADAMTS13 activities of 5, 6, and 12 percent and all had an inhibitor; the patient with no response was subsequently determined to have Rocky Mountain spotted fever.

CONCLUSION: Twice-daily plasma exchange was typically considered in acutely ill patients who had initially responded but then severe thrombocytopenia recurred, often with new neurologic abnormalities, while continuing daily plasma exchange. In three patients, twice-daily plasma exchange appeared to be beneficial. In most patients, a benefit of twice-daily plasma exchange could not be clearly documented because other treatments were initiated or intensified.

Twice-daily plasma exchange has been described as intensive treatment for patients with thrombotic thrombocytopenic purpura (TTP) who do not initially respond to daily plasma exchange treatment or who subsequently deteriorate while on daily plasma exchange.[1-4] There have been anecdotes of success for more than 28 years, and although twice-daily plasma exchange continues to be used, there is no clear evidence for its effectiveness.[1-4] The rationale for twice-daily plasma exchange is that infusion of plasma is a key component of plasma exchange treatment[5] and that a greater volume of infused plasma may provide greater benefit.[6,7]

Twice-daily plasma exchange procedures, however, may not always be possible because they require a great time commitment for apheresis nurses and large volumes of plasma. Estimates from our experience are that a single plasma exchange procedure, including the time for preparation and travel to the patient's hospital, may require up to 6 hours. Furthermore, some observations have not supported the concept that greater volumes of plasma have greater efficacy. A survey of US medical centers reported similar rates of mortality, relapse, and remission for

ABBREVIATIONS: HUS = hemolytic-uremic syndrome; TTP = thrombotic thrombocytopenic purpura.

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patients treated with 1.0 to 1.3 plasma volumes per exchange procedure compared to 1.5 to 2.0 plasma volumes.[8] No recommendations for twice-daily plasma exchange are made in current statements and guidelines because of the absence of evidence for its effectiveness.[9,10]

Twice-daily plasma exchange treatment has been regularly although infrequently used in our community for patients whose thrombocytopenia has not responded to daily plasma exchange. It is also used in patients who develop recurrent thrombocytopenia while continuing daily plasma exchange. To evaluate our experience, we analyzed the outcomes of 31 episodes of TTP in 28 patients who were treated with twice-daily plasma exchange.

MATERIALS AND METHODS

The Oklahoma TTP-HUS Registry

This report describes the experience of the Oklahoma TTP-HUS (hemolytic-uremic syndrome) Registry from its inception in January 1, 1989, through December 31, 2006. The Registry includes all consecutive patients for whom the Oklahoma Blood Institute was requested to provide plasma exchange treatment for patients with a diagnosis of TTP or HUS.[11,12] The Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in central, western, and southeastern Oklahoma. The standard practice in our region is to treat all adult patients who are diagnosed as TTP or HUS, as well as children with TTP or atypical HUS, with plasma exchange. Therefore, we identify and enroll all consecutive patients in whom the diagnosis of TTP or HUS was made and plasma exchange treatment was requested.

Patients were assigned in a hierarchical, sequential order, based on the assessment during their first episode, to one of six clinical categories related to potential etiologies or associated conditions, as previously described:[11] 1) posthematopoietic stem cell transplantation, 2) pregnant or postpartum, 3) drug association, 4) bloody diarrhea prodrome, 5) presence of an additional or alternative disorder which may have caused the presenting features, and 6) idiopathic, if none of the criteria for the previous five clinical categories was fulfilled. The Registry receives annual approval by the institutional review boards of the University of Oklahoma Health Sciences Center and participating hospitals.

Definitions of clinical outcomes

In all patients treated with plasma exchange, a response was defined as a PLT count of at least 150×10^9 per L achieved during the plasma exchange treatment or within 1 week of stopping treatment. Exacerbation was defined as recurrent thrombocytopenia after a response plus resumption of daily plasma exchange treatment after at least 1 day of no plasma exchange. Remission was defined as no evidence for TTP for 30 days after the last plasma exchange treatment. Relapse was defined as recurrence of TTP after a remission; survival was defined as living more than 30 days after the last plasma exchange treatment.[11,12]

Plasma exchange treatment

Our standard treatment is one plasma exchange treatment per day with one plasma volume per exchange. Fresh-frozen plasma (FFP), 24-hour plasma, or cryosupernatant plasma are used based on product availability rather than on a patient's clinical condition. In some patients the volume of plasma for once-daily plasma exchange was increased to 1.5 plasma volumes. This was done when a patient was not responding to once-daily plasma exchange but the effort required for twice-daily plasma exchange was not deemed necessary or was not logistically possible. For this analysis, 1.0 and 1.5 plasma volume exchange treatments were grouped together and considered as a single daily plasma exchange.

In general, twice-daily plasma exchange was used for acutely ill patients who initially responded to daily plasma exchange but then developed severe recurrent thrombocytopenia. Recurrent thrombocytopenia was often associated with new neurologic abnormalities, despite continuing daily plasma exchange and glucocorticoid treatment. Twice-daily plasma exchange was also used in patients with a confident diagnosis of idiopathic TTP who did not respond after many days of initial treatment with daily plasma exchange plus glucocorticoids, but this situation occurred less frequently. Patients were changed back to once-daily plasma exchange when the PLT count responded to greater than 30×10^9 to 50×10^9 per L. Patients who had an exacerbation after stopping daily plasma exchange were restarted on daily plasma exchange treatment.

Assessment of response to twice-daily plasma exchange

The response to twice-daily plasma exchange was determined by the PLT count. Data for each patient were analyzed with a computer program graph (Microsoft Excel, Microsoft Corp., Redmond, WA) to determine the relationship among PLT counts, plasma exchange treatments, and other treatments. With these graphs, each of the six authors independently judged the responses to twice-daily plasma exchange for each episode. Two of the authors were involved in the care of the patients; the other authors were involved only in data analysis.

Because of the subjectivity of the authors' judgments and the inherent weakness of a retrospective observa-

tional study, we established a priori very stringent criteria for a definite response to the initiation of twice-daily plasma exchange (Table 1). Criteria for a definite response included: 1) a PLT count increase after initiation of twice-daily plasma exchange at least twice during the treatment course for a single episode of TTP, without initiation or intensification of other treatments (decreasing the possibility that the PLT count increase was merely incidental to the initiation of twice-daily plasma exchange) and 2) consensus of all six authors required after independent review. Because of the variability in both the magnitude of the PLT count responses and the times when a response occurred after the beginning of twice-daily plasma exchange, no strict criteria were established to define a response. A PLT count increase greater than 50×10^9 per L in less than 5 days was usually considered to be a response.

Patients were defined as having no response when all authors agreed that there was no PLT count increase following initiation of twice-daily plasma exchange. The remainder of the patients were judged to have had a possible response. Criteria for a possible response were 1) a PLT count increase after initiation of twice-daily plasma exchange that occurred only once during a course of treatment without initiation or intensification of other treatments and/or 2) one or more PLT count increases after initiation of twice-daily plasma exchange that were accompanied by initiation or intensification of other treatments. Patients were determined to have a possible response to twice-daily plasma exchange either when all authors agreed that the criteria to define a possible response were met or when the opinions of the authors were not consistent, with judgments divided between a definite and possible response or between a possible response and no response.

TABLE 1. Criteria for assessing the response to twice-daily plasma exchange in patients with TTP

Definite response	PLT counts increased with the initiation of twice-daily plasma exchange, decreased when once-daily plasma exchange was resumed, and then increased again with twice-daily plasma exchange, during the course of treatment for a single episode. No other concurrent treatments for TTP were either initiated or changed.
Possible response	PLT counts increased with the initiation of twice-daily plasma exchange but only one time during the course of treatment for a single episode, and/or PLT counts increased with twice-daily plasma exchange one or more times but also with initiation of new treatments or intensification of existing treatments.
No response	PLT counts did not change with the initiation of twice-daily plasma exchange.

ADAMTS13 measurements

Serum samples have been collected immediately before the initial plasma exchange treatment since November 13, 1995, on 242 (92%) of 268 patients' initial episodes. ADAMTS13 activity has been measured by B. Lämmle and J. Kremer Hovinga (Inselspital, University of Berne, Berne, Switzerland).[13,14] Results of the ADAMTS13 activity measurements were not known at the time of the patients' treatment for their initial episode.

RESULTS

Patients

During 18 years of The Oklahoma TTP-HUS Registry, 1989 through 2006, 34 patients were treated with twice-daily plasma exchange for 37 episodes of TTP. The goal of our analysis was to determine if twice-daily plasma exchange was beneficial in patients whose thrombocytopenia had not responded to daily plasma exchange or in whom thrombocytopenia recurred after an initial response in spite of continued daily plasma exchange. Consequently six patients whose treatment for TTP began with twice-daily plasma exchange were excluded from this analysis because their initial therapy included twice-daily plasma exchange, not allowing a determination by our criteria. In this report we describe the analysis of twice-daily plasma exchange for 31 episodes of TTP in 28 patients. Three patients, two with idiopathic TTP and one with TTP associated with scleroderma, were treated with twice-daily plasma exchange during two separate episodes of TTP.

Twice-daily plasma exchange was first used for a patient in the Oklahoma TTP-HUS Registry in 1991. One to seven episodes per year were treated with twice-daily plasma exchange during 13 of the 16 years, from 1991 through 2006. Six patients have been treated with twice-daily plasma exchange in the past 4 years, one or two patients per year, indicating that twice-daily plasma exchange continues to be used even though immunosuppressive agents, including glucocorticoids and rituximab, have been used more frequently in recent years.

Of the 368 consecutive patients enrolled in the Registry from 1989 through 2006, 331 patients who received two or more once-daily plasma exchange treatments and lived for 3 or more days could possibly have received twice-daily plasma exchange for unresponsive thrombocytopenia and been evaluated for response. The other 37 patients were not treated with plasma exchange (some died before plasma exchange could be initiated; in some, plasma exchange was withheld because of an initial response to plasma infusion and/or glucocorticoids), had only a single plasma exchange treatment, or began their treatment with twice-daily plasma exchange. Therefore, the 28 patients treated with twice-daily plasma exchange and analyzed in the report represent 8.5 percent of all 331 patients who could have received twice-daily plasma exchange for

refractory TTP; the 31 episodes represent 8.2 percent of these patients' 378 episodes that were treated with plasma exchange. In these 31 episodes, twice-daily plasma exchange was initiated on Days 2 to 27 (median, Day 6; Day 1 was the first day of plasma exchange treatment). Twice-daily plasma exchange treatment was used for 1 to 21 days (median, 3 days); 13 episodes were treated with more than one course of twice-daily plasma exchange (two to four courses; median, two courses). The 31 episodes of twice-daily plasma exchange were treated at seven different hospitals by 13 different physicians.

Response to twice-daily plasma exchange

Twelve patients (13 episodes) were treated with two or more courses of twice-daily plasma exchange and therefore were eligible to be judged as having a definite response. Of these 12 patients, 3 patients (three episodes) were judged to have definite responses to twice-daily plasma exchange; their clinical courses are illustrated in Figs. 1 through 3. One of these three patients (Patient 1) had a second episode treated with twice-daily plasma exchange that was judged to have a possible response because the opinions of the authors were divided between definite and possible responses.

Only one patient (one episode) was judged to have no response by all six authors. The other 26 episodes in 24 patients were judged to have possible responses to twice-daily plasma exchange.

Of the 27 episodes judged to have a possible response, 8 episodes were judged to have possible responses by all six authors. Among the other 19 episodes, 10 episodes were judged to have a definite response by one or more authors but other authors judged the response as only possible. The 27 episodes that were defined as possible responses were treated with one to four courses of twice-daily plasma exchange (median, one course). Among all 41 courses of twice-daily plasma exchange, there was no PLT count response with 3 courses, a PLT count response without a change in other treatment occurred 11 times, and a PLT count response when other treatments were initiated or changed occurred 27 times. The three patients in whom a course of twice-daily plasma exchange resulted in no PLT count response each had another course of twice-daily plasma exchange with a PLT count response. The 11 episodes in which a course of twice-daily plasma exchange resulted in a PLT count response

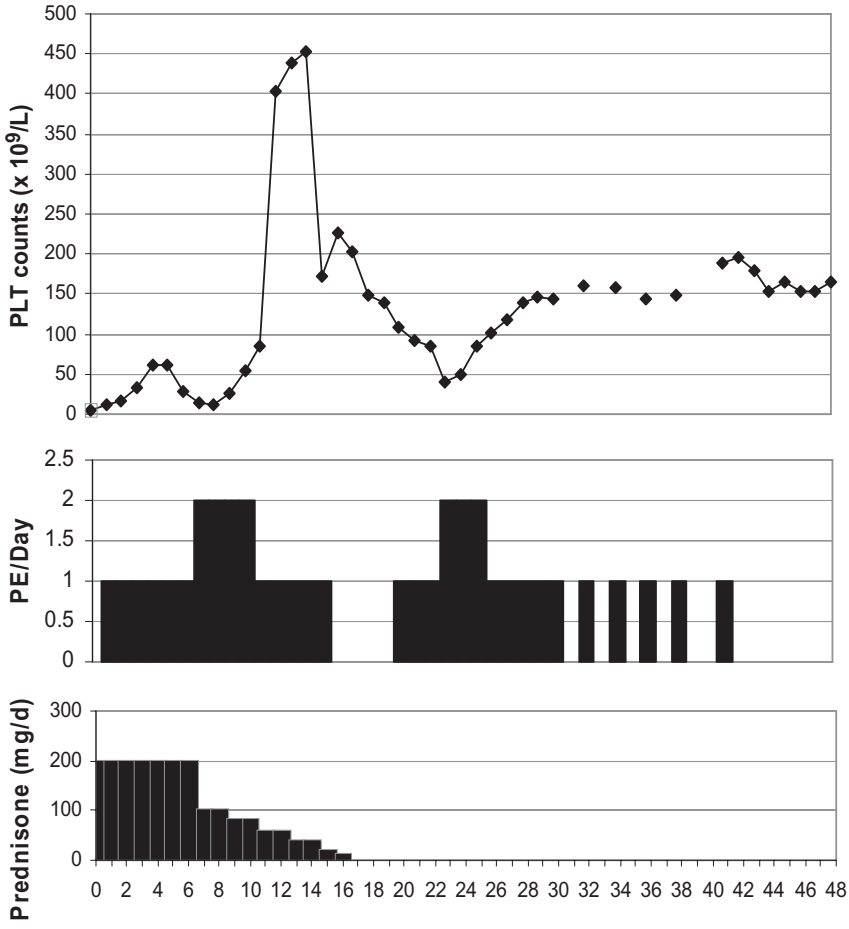

Fig. 1. A 40-year-old white woman was admitted with her first episode of TTP in 1997. She was treated with prednisone, 200 mg per day, and the following day began once-daily plasma exchange (PE) treatments. Her PLT count increased from 6×10^9 to 62×10^9 per L on Day 4 (Day 1 is defined as the day of the first plasma exchange) but then decreased to 16×10^9 per L on Day 7 when she developed aphasia and became obtunded. Her PLT count responded to twice-daily plasma exchange treatments while steroids were being tapered, because of hyperglycemia. Plasma exchange treatments were stopped on Day 16 and she was discharged from the hospital. She was readmitted on Day 20 with *Staphylococcus aureus* sepsis and her PLT count decreased again. She did not respond to 3 days of appropriate antibiotics and once-daily plasma exchange treatments but then responded again to twice-daily plasma exchange treatments. Steroid treatment was not resumed because of the sepsis. She received FFP throughout her course of treatment. Her ADAMTS13 activity was 5 percent with an inhibitor. She relapsed 4 months later and had a possible response to 1 day of twice-daily plasma exchange. She had three more episodes over the next 5 years that did not require twice-daily plasma exchange treatments. She has now been in remission for 5 years.

without a change in other treatment only had one such response and therefore did not qualify for a definite response.

All patients judged to have a possible response had an increased PLT count after initiation of at least one course of twice-daily plasma exchange. The two different criteria used to define a possible response to twice-daily plasma exchange are illustrated by the clinical courses of patients illustrated in Figs. 4 and 5. The patient in Fig. 4 was judged to have a PLT count response to twice-daily plasma exchange with no change in other treatments. Because she only had a single course of twice-daily plasma exchange treatment for her episode of TTP, however, she was classified as having a possible response. The patient in Fig. 5 had a critical and complicated course; she may have responded to each of her four courses of twice-daily plasma exchange, but each time changes in her other treatments could also have been responsible for the increased PLT counts. Her course was more common among the patients who were judged to have possible responses. Initiation or intensification of other treatments in addition to beginning twice-daily plasma exchange was a common practice in these critically ill patients and inevitably confounded interpretation of the effect of twice-daily plasma exchange.

All three patients with a definite response to twice-daily plasma exchange achieved a remission; the patient with no response died. Twenty (83%) of the 24 patients judged to have a possible response achieved a remission; the other 4 patients died.

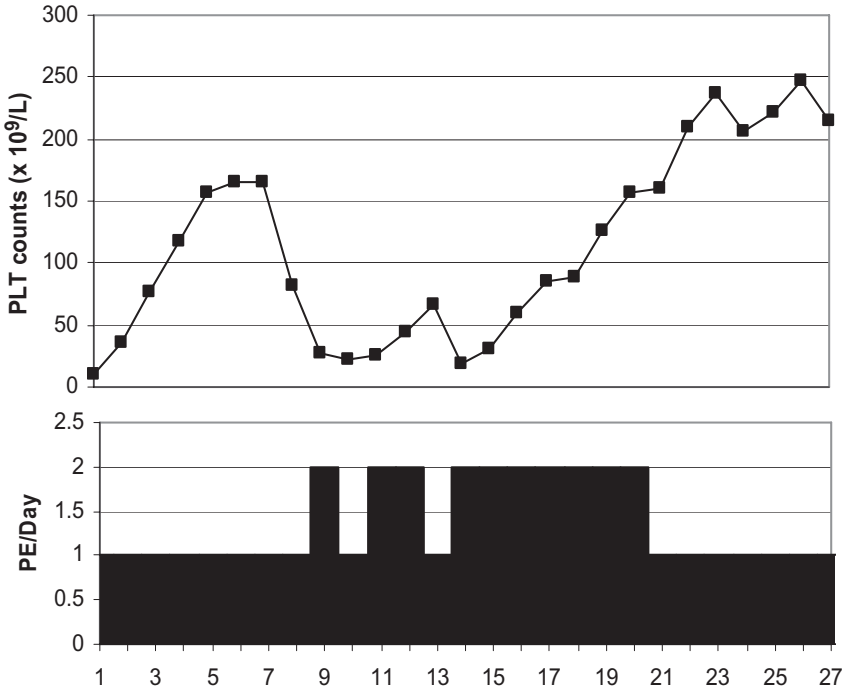

Fig. 2. A 68-year-old white woman was admitted with her first episode of TTP in 1999. Her PLT count increased from 6×10^9 to 157×10^9 per L on Day 5 with once-daily plasma exchange (PE) treatments but then decreased to 27×10^9 per L on Day 9 while continuing once-daily plasma exchange. She had no neurologic abnormalities. Her PLT count responded to twice-daily plasma exchange treatments on two occasions. She did not receive any immunosuppressive therapy and steroids were withheld because of severe diabetes mellitus. She was treated with cryoprecipitate-poor plasma through Day 12 when she was changed to FFP for the remainder of her treatment. Her ADAMTS13 activity was 6 percent with an inhibitor. She has been in remission without a relapse for 8 years.

TABLE 2. Comparison of patients treated with twice-daily plasma exchange to patients treated only with once-daily plasma exchange

Demographics, clinical features	Twice-daily plasma exchange (n = 28)	Once-daily plasma exchange (n = 303)	p Value
Age (years, median)	50	46	0.236
Sex (% female)	79	71	0.412
Race (% black)	18	19	0.836
Idiopathic clinical category (%)	57	37	0.071
ADAMTS13 activity			
All patient categories* (% < 10%)	46 (11/24)	18 (38/210)	0.002
Idiopathic patients* (% < 10%)	71 (10/14)	32 (29/78)	0.017

* ADAMTS13 activity was measured in 24 patients treated with twice-daily plasma exchange and 210 patients treated with once-daily plasma exchange.

Patient characteristics

The age, sex, and race of the 28 patients treated with twice-daily plasma exchange were not different from the patients in the Registry who were not treated with twice-daily plasma exchange (Table 2). The clinical category and frequency of severe ADAMTS13 deficiency in the 28 patients treated with twice-daily plasma exchange, however, were distinct from the patients in the Registry who were not treated with twice-daily plasma exchange (Table 2). Although each of the six clinical categories of TTP presentation was represented among these 28 patients, 16 (57%) of the 28 patients treated with twice-daily plasma exchange compared to 112 (37%) of the 303 patients who were not treated with twice-daily plasma exchange were in the idiopathic category ($p = 0.071$). Eleven (46%) of the 24 patients treated with twice-daily plasma exchange in whom ADAMTS13 activity was measured had severe ADAMTS13 deficiency (activity, <10%)

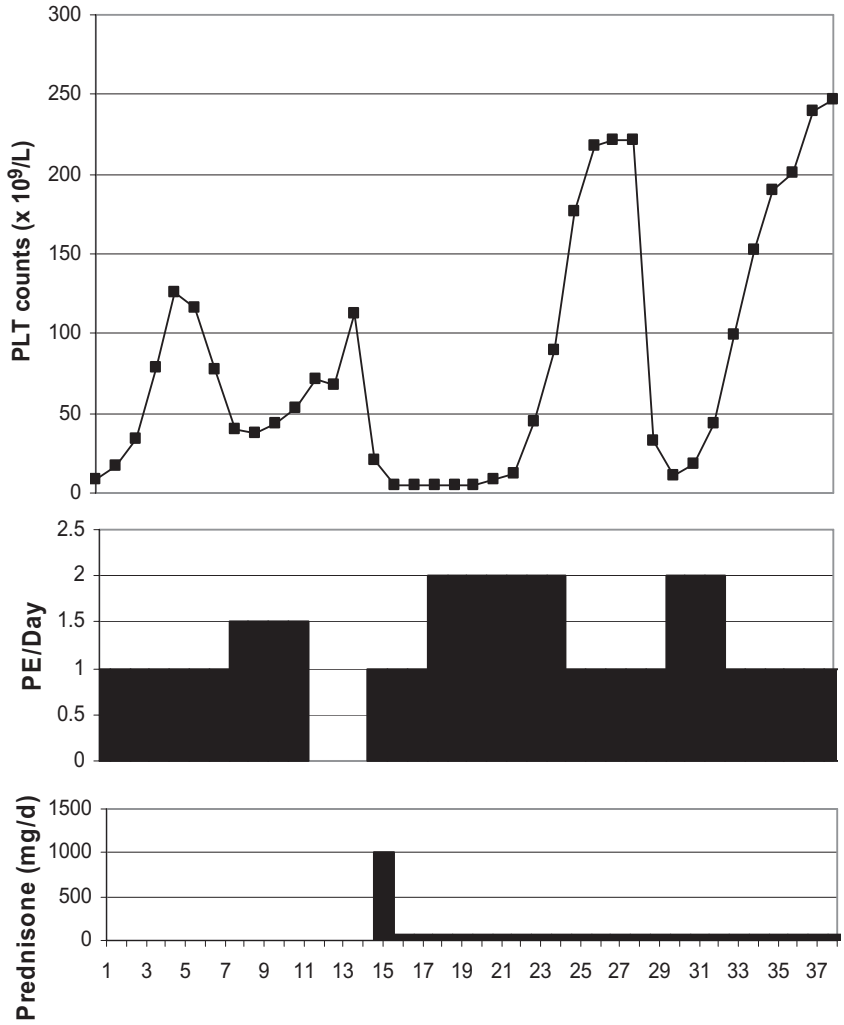

Fig. 3. A 56-year-old white woman was admitted with her first episode of TTP in 2000. Her PLT count increased from 7×10^9 to 126×10^9 per L on Day 5 with once-daily plasma exchange treatments but then decreased to 40×10^9 per L while continuing once-daily plasma exchange. She had no neurologic abnormalities. She was then treated with 4 days of once-daily plasma exchange with 1.5 plasma volumes per exchange. Although she responded, she had an anaphylactic reaction to plasma on Day 11 and the plasma exchange treatments were stopped for 3 days. When plasma exchange was resumed on Day 15 because her PLT count decreased to 10×10^9 per L, she was given 1000 mg of methylprednisolone for 1 day, then prednisone, 60 mg per day. She received twice-daily plasma exchange on two occasions, each followed by a PLT count response. She was treated with FFP for her first 11 days and then changed to cryoprecipitate-poor plasma for the remainder of her course when plasma exchange treatment was resumed on Day 15. Her ADAMTS13 activity was 12 percent with an inhibitor. She has not relapsed and has been in remission for 7 years.

compared to 38 (18%) of the 210 patients who were not treated with twice-daily plasma exchange ($p = 0.002$). Ten (71%) of the 14 patients with idiopathic TTP in whom ADAMTS13 activity was measured had severe ADAMTS13 deficiency (activity, <10%) compared to 29 (32%) of the 78 patients with idiopathic TTP who were not treated with twice-daily plasma exchange ($p = 0.017$). ADAMTS13 activity was 12 to 20 percent in the other 4 patients with idiopathic TTP who were treated with twice-daily plasma exchange. Among the 12 patients treated with twice-daily plasma exchange who presented with clinical categories other than idiopathic, ADAMTS13 was measured in 11 and all had activity of at least 35 percent except for one woman in whom TTP occurred postpartum whose ADAMTS13 activity was less than 5 percent.

The three patients who had a definite response to twice-daily plasma exchange were all in the idiopathic category and had ADAMTS13 activities of 5, 6, and 12 percent. ADAMTS13 inhibitory activity was demonstrated in all three patients. The one patient who had no response to twice-daily plasma exchange was subsequently diagnosed with Rocky Mountain spotted fever; his ADAMTS13 activity was 70 percent.

DISCUSSION

The appropriate management for patients who fail to respond to initial treatment with daily plasma exchange or who exacerbate with recurrent thrombocytopenia after an initial response is uncertain. These patterns of PLT count response may be common, even among patients who ultimately achieve a remission. A recent study documented that PLT counts initially decreased in 28 percent of patients when daily plasma exchange treatments were begun; an additional 19 percent of patients had an initial PLT count increase but then their PLT counts decreased to less than 100×10^9 per L with continued daily plasma exchange.[15] Although recovery with no change of treatment was documented in some of these patients,[15] clinical deterioration in addition to worsening thrombocytopenia may occur in other patients. Severe exacerbations of TTP may occur even in patients who are treated concurrently with glucocorticoids and more intensive immunosuppression.[16,17] In these patients, treatment with twice-daily plasma exchange may be considered. There is currently, however, no published evidence that twice-daily plasma exchange is more effective than daily plasma exchange, and the

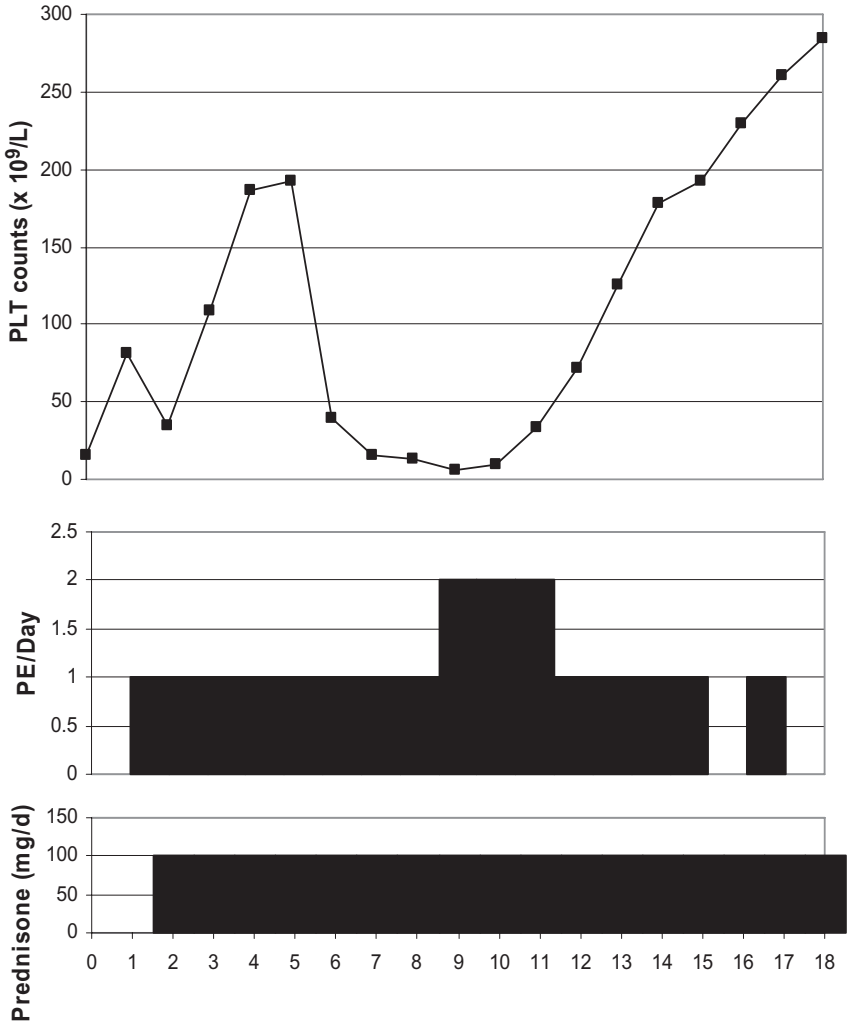

Fig. 4. A 46-year-old black woman was admitted with her first episode of TTP in 2004. Her PLT count increased from 16×10^9 to 186×10^9 per L on Day 4 with once-daily plasma exchange treatments plus prednisone, 100 mg per day. Her PLT count decreased to 16×10^9 per L on Day 7 while continuing once-daily plasma exchange and prednisone, coincident with the occurrence of *S. aureus* sepsis. She had no neurologic abnormalities. Her PLT count responded to twice-daily plasma exchange treatments, which were begun on Day 9, as well as to treatment of her sepsis. She was treated with cryoprecipitate-poor plasma throughout her course. Her ADAMTS13 activity was less than 5 percent with an inhibitor. She relapsed 6 months later but now has been in remission for 3 years.

great personnel effort and resource utilization required for twice-daily plasma exchange limit its feasibility.

Our 18-year experience suggests that twice-daily plasma exchange may be effective treatment for some patients with TTP who are unresponsive to daily plasma exchange or who exacerbate with continuing daily plasma exchange treatments. To assess the response to twice-daily plasma exchange we established very stringent criteria to define a definite response, that required a PLT count response after initiation of twice-daily plasma exchange at least twice during the course of treatment for an episode of TTP, without initiation or intensification of other treatments. We also required that all six authors independently agreed that the criteria for a definite response were met. With these rules, 3 of the 28 patients (3 of 31 episodes) had a definite response to twice-daily plasma exchange. Although this pattern of increasing and decreasing PLT counts may also be observed in patients with no change in their treatment,[15] the responses in these patients appeared to be related to the initiation of twice-daily plasma exchange treatment. Other patients who were defined as having only a possible response may also have benefited from twice-daily plasma exchange, but changes of other treatments prevented a clear interpretation (Fig. 5) or they only responded once during the course of their TTP episode (Fig. 4). Of the 27 episodes judged to have a possible response, only 10 episodes were treated with two or more courses of twice-daily plasma exchange and were therefore potentially eligible to be judged as a definite response. Appropriately, the one patient in our series who clearly had no benefit from twice-daily plasma exchange was subsequently documented to have an alternative etiology for his fatal illness, Rocky Mountain spotted fever.

Patients who required twice-daily plasma exchange were more likely to have ADAMTS13 deficiency. This is consistent with previous observations that these patients may be more refractory to standard treatments.[16,17] The three patients who had a definite response to twice-daily plasma exchange all had ADAMTS13 deficiency (activity levels of 5, 6, and 12%) with a demonstrable inhibitor, suggesting that these patients may also have the greatest potential for benefit from this intensive procedure. It is possible that these patients may have recovered without twice-daily plasma exchange or even without other modifications of their treatment.[15] In these patients, however, the recurrent thrombocytopenia was sudden and severe, and as seen in Patient 1 (Fig. 1) was accompanied by acute neurologic abnormalities.

Our patients treated with twice-daily plasma exchange were not demographically different from patients not treated with twice-daily plasma exchange and were treated at multiple hospitals by different physicians.

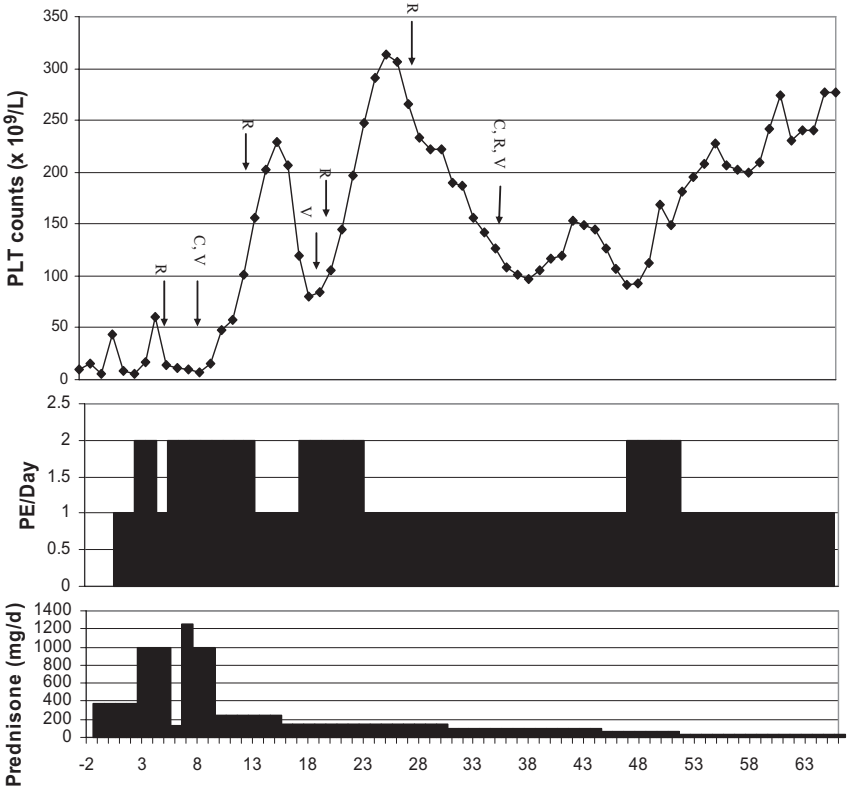

Fig. 5. A 63-year-old white woman was admitted with her first episode of TTP in 2006. She was treated with 375 mg per day methylprednisolone, together with daily plasma exchange but her PLT count decreased to 6×10^9 per L on Day 3. On Day 4 she developed severe aphasia; methylprednisolone was increased to 1000 mg per day and twice-daily plasma exchange was begun. She improved after 2 days of twice-daily plasma exchange but then after 1 day of once-daily plasma exchange her PLT count decreased to 14×10^9 per L and she became unresponsive and hypotensive. Twice-daily plasma exchange and high-dose methylprednisolone were resumed and rituximab (R) was added. Two days later her PLT count remained 7×10^9 per L and she had multiple grand mal seizures; cyclophosphamide (C) and vincristine (V) were added to her treatment. She gradually recovered, although a fourth course of twice-daily plasma exchange was performed when her PLT count decreased again from 229×10^9 per L on Day 16 to 80×10^9 per L on Day 19; although she had no neurologic symptoms, the change to twice-daily plasma exchange treatment was prompted by her prior critical course. Both FFP and 24-hour plasma were used throughout her course. Her ADAMTS13 activity was less than 5 percent with an inhibitor. She has not relapsed during the subsequent 16 months.

These observations support the interpretation that patients were treated with twice-daily plasma exchange because of the critical course of their TTP, not because of different patterns of practice in our community.

Although our retrospective, uncontrolled observations do not provide strong evidence for the benefit of treatment with twice-daily plasma exchange, we interpret these data to support our continuing practice of twice-daily plasma exchange, in addition to other intensive adjunctive treatments, for patients who are critically ill with TTP and unresponsive to other treatments. Twice-daily plasma exchange is considered in patients with idiopathic TTP or in whom severe ADAMTS13 deficiency is suspected. These patients are generally expected to respond to plasma exchange treatment. When these patients remain severely thrombocytopenic while on daily plasma exchange plus glucocorticoids for many days or when severe thrombocytopenia recurs after an initial response in spite of continued daily plasma exchange and glucocorticoids, twice-daily plasma exchange may be considered. A randomized clinical trial to document the efficacy of twice-daily plasma exchange would be difficult in these patients for two reasons: 1) Usually multiple treatment modalities are used to attempt to reverse a critical course, confounding the ability to determine the effectiveness of twice-daily plasma exchange. 2) TTP is an uncommon syndrome and in our experience less than 10 percent of patients with TTP are considered for treatment with twice-daily plasma exchange treatment. It is possible that with the greater use of more intensive immunosuppressive treatments earlier in the course of TTP,[18,19] twice-daily plasma exchange may be considered less often.

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