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Chronic Relapsing Thrombotic Thrombocytopenic Purpura: Role of Therapy With Cyclosporine

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Relapsing thrombotic thrombocytopenic purpura (TTP) is a rare disorder with most individuals experiencing 1 to 5 relapses. We report a patient with 18 episodes of thrombotic thrombocytopenic purpura (TTP), the highest number of relapses thus far described. The last 11 episodes were treated with regimens containing cyclosporine. The patient's medical record was reviewed for pertinent clinical, laboratory, and treatment data. We summarized various parameters for each episode and compared characteristics of relapses treated with vs. without cyclosporine. The initial episode of TTP was unusual in that it failed to respond to plasmapheresis, glucocorticoids, and fresh frozen plasma (FFP). It remitted only following splenectomy. Episodes 2–7 responded to FFP plus prednisone. Episode 8 failed to respond to prednisone plus FFP but remitted promptly with cyclosporine plus prednisone. Subsequently, 2 relapses responded to cyclosporine alone, 2 to cyclosporine plus FFP, 4 to cyclosporine plus prednisone ± FFP, and 2 to cyclosporine, FFP, prednisone, and plasma exchange. There was no difference in remission duration, or in severity or duration of relapses treated with vs. without cyclosporine. Use of cyclosporine, however, significantly decreased the requirement for prednisone and the length of maintenance therapy; thus it is effective mainly as an adjunctive therapy for TTP. Am. J. Hematol. 57:57–61, 1998. © 1998 Wiley-Liss, Inc.†

Key words: thrombotic thrombocytopenic purpura; TTP; cyclosporine; chronic relapsing TTP

INTRODUCTION

Idiopathic thrombotic thrombocytopenic purpura (TTP) is a rare (about 1 case per 1,000,000 population per year) disorder of unknown etiology characterized by thrombocytopenia and microangiopathic hemolytic anemia [1–3]. About 75% of patients have neurological and/or renal dysfunction and 20% have fever [3]. Sixteen (16%) to 69% of patients have a chronic relapsing course with most individuals relapsing 1 to 5 times [3,4]. The highest number of TTP relapses previously described in a single patient is 11 [5].

Plasma exchange is the primary mode of therapy with fresh frozen plasma (FFP) and glucocorticoids being effective for some patients with mild episodes [3]. The role of antiplatelet agents, splenectomy, and intravenous immunoglobulin is less well defined [3].

We describe a patient with chronic relapsing TTP who had 18 episodes over 18 years. The first episode was initially treated with 36 plasma exchange procedures, intermittent FFP, prednisone, and vincristine over 96 days. However, remission occurred only following splenectomy. The subsequent 17 episodes responded to various immunomodulatory treatments. Six episodes responded to FFP plus prednisone, 2 responded to cyclosporine alone, 2 to cyclosporine plus FFP, 5 to cyclosporine, prednisone ± FFP, and 2 to cyclosporine, prednisone,

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FFP, and plasma exchange. Comparison of clinical and laboratory data of episodes treated with vs. without cyclosporine-containing regimens indicate that cyclosporine has a steroid sparing effect and allowed for shorter duration of maintenance therapy. Response to cyclosporine has been reported in 8 other patients [6–10].

MATERIALS AND METHODS

From a review of the patient's record we compared clinical and laboratory parameters during relapses treated with vs. without cyclosporine. The Student's *t*-test or chi-square was applied to determine whether differences were significant. A P value of <0.05 was considered significant.

CASE REPORT

A 50-year-old male presented in May 1980 with thrombocytopenia, microangiopathic hemolytic anemia, fever, confusion, left hemi-paresis, dysarthria, and seizures. Table I illustrates nadir platelet count, and peak lactate dehydrogenase (LDH) and reticulocyte count. Peak serum creatinine was 1.8 mg/dL and decreased to 0.8 mg/dL after remission. Prothrombin time, activated partial thromboplastin time, and fibrinogen were normal. No sustained response occurred with glucocorticoids, 36 separate plasma exchange procedures, aspirin, dipyridamole, and vincristine. On day 98, one day following splenectomy, platelets improved to $115 \cdot 10^9$/L. Resolution of neurological symptoms and fever followed. A transitory decrease in platelets on days 104–106, which occurred after reduction in prednisone and interruption of FFP, responded to an increase of prednisone and FFP.

All relapses were characterized by an acute drop in platelets from $405 \pm 8 \cdot 10^9$/L (mean ± SE, n = 240) to $<57 \cdot 10^9$/L (except episodes 10 and 18, platelet nadirs 111 and $166 \cdot 10^9$/L, respectively), fragmented red cells on blood smears, and a rise in LDH and reticulocytes. During relapses the patient had mental confusion and ecchymoses at venipuncture and insulin injection sites. For each episode, Table I summarizes date of diagnosis, date of resolution (first day of sustained platelets $>175 \cdot 10^9$/L), episode duration, days since resolution of last episode (interval between relapses), number of days off therapy prior to relapse (interval from discontinuation of maintenance treatment to relapse), lowest platelet count, highest LDH and reticulocytes, and therapy up until episode resolution. For all episodes, the mean (±SE) duration was 31 ± 8 days, interval between relapses 335 ± 44 days, time off therapy prior to relapse 156 ± 37 days, nadir platelets $42 \pm 9 \cdot 10^9$/L, peak LDH 1,085 ± 123 IU/L, and peak reticulocytes $372 \pm 60 \cdot 10^9$/L. During episodes creatinine was 2.1 ± 0.07 mg/dL (n = 185) vs. 1.8 ± 0.04 (n = 178, $P < 0.001$) during remission. The most recent episode resolved on June 4, 1997.

Treatment of Relapses

The second and third episodes responded promptly to 3 and 4 days, respectively, of concurrent prednisone plus FFP. Episodes 4, 6, and 7 responded to 20–64 days of daily prednisone and intermittent FFP. Episode 5 failed to respond to 20 days of intermittent FFP but remitted after an additional 48 days with addition of daily prednisone. The eighth episode did not respond to 9 days of FFP and an additional 19 days of daily prednisone plus intermittent FFP. It responded 4 days after addition of cyclosporine 500 mg po daily. Episode 9 failed to respond to 8 days of daily cyclosporine plus intermittent FFP, and to 22 days of daily prednisone plus intermittent FFP. It remitted after an additional 12 days of daily cyclosporine and prednisone. Episodes 10 and 18, mild relapses, responded to 21 and 15 days, respectively, of daily cyclosporine. Episodes 11, 12, and 15 failed to respond to 7–15 days of daily cyclosporine. They remitted after an additional 12–15 days of combined cyclosporine, prednisone, and intermittent FFP. Episode 13 failed to respond to 15 days of daily cyclosporine, but remitted after 22 days of cyclosporine plus intermittent FFP. Episode 14 responded promptly to 3 days of daily cyclosporine and FFP. Episode 16 failed to respond to 11 days of cyclosporine, prednisone, and FFP. It remitted 4 days following 2 plasma exchange procedures while continuing cyclosporine and prednisone. Episode 17 promptly responded in 4 days to FFP, one plasma exchange procedure, cyclosporine, and prednisone. Clinical characteristics of relapses treated with vs. without cyclosporine (Table II) indicated that use of cyclosporine resulted in decreased ($P = 0.005$) duration of maintenance prednisone therapy as well as a shortened ($P = 0.011$) total duration of maintenance therapy. All other parameters compared were similar. Our results indicate that mild relapses with peak LDH of <920 IU/L and nadir platelet count $> 34 \cdot 10^9$/L respond to cyclosporine ± FFP ($P = 0.008$), while more severe relapses require additional therapy.

The dose of FFP was 4.0 ± 0.1 U per infusion. FFP was discontinued when platelets began rising ($102 \pm 16 \cdot 10^9/\mu$L) and restarted for significant reduction in count. Prednisone was begun at 50 ± 5 mg/day. Dose reduction began when platelets were above $300 \cdot 10^9$/L, and was increased to the previously effective level for reductions in platelets. Cyclosporine was started at 400 ± 30 mg/day. Blood was monitored to maintain trough levels at 150–250 ng/mL. Cyclosporine was tapered and discontinued following discontinuation of prednisone using criteria similar to prednisone. Possible toxicity from cyclosporine was one episode of Herpes zoster following episode 8, and elevation in serum creatinine to

TABLE I. Date of Diagnosis and Resolution (First day of sustained platelets > 175 · 10^9/L), Episode Duration, Days Since Last Episode (Number of days since resolution of previous episode to diagnosis of relapse), Days Since Last Therapy (Number of days from discontinuation of maintenance therapy to diagnosis of relapse), Lowest Platelet Count, Highest LDH and Reticulocyte Count (Retic), and Treatment for Each Episode of TTP*

No.	Date of diagnosis	Date of resolution	Episode duration (days)	Days since last episode	Days since last therapy	Lowest platelet	Highest LDH	Highest Retic	Therapy	Days[a]
1	5/2/80	9/17/80	138			2	2,040	1,275	PRED	3–138
									EX	12–81
									FFP	64–136
									VCR	85,93
									SPL	97
2	4/8/81	4/10/81	3	203	0	26	710	Not done	FFP	1,2
									PRED	1–3
3	10/27/81	10/30/81	4	199	13	46	888	453	FFP	1,2
									PRED	1–4
4	8/18/83	9/7/83	20	657	484	52	994	455	FFP	1,2
									PRED	2–20
5	11/16/84	1/23/85	68	436	256	47	698	336	FFP	1–3,13–26,29,31,35
									PRED	20–68
6	9/3/86	9/24/86	21	588	315	30	819	254	FFP	1,2
									PRED	1–21
7	10/12/87	12/15/87	64	383	95	34	904	240	FFP	1
									PRED	1–64
8	1/9/89	2/10/89	32	391	313	35	1,196	486	FFP	1–9,12,14,15,17,22
									PRED	10–32
									CYA	29–32
9	6/13/90	7/25/90	42	488	217	27	952	287	FFP	1,2,6,7,14–19,23–32
									PRED	9–42
									CYA	1–8,30–42
10	3/11/92	4/1/92	21	595	476	111	399	193	CYA	7–21
11	7/6/92	8/5/92	30	96	26	21	1,667	419	CYA	1–30
									FFP	16–17
									PRED	16–30
12	11/10/93	11/29/93	19	462	70	22	1,677	416	CYA	1–19
									FFP	3,8,10,11
									PRED	7–19
13	11/28/94	1/4/96	37	364	75	56	586	254	CYA	1–37
									FFP	16,17,30,32
14	4/6/95	4/10/95	4	92	22	35	862	270	FFP	1–3
									CYA	1–4
15	8/16/95	9/3/95	19	128	28	31	921	241	CYA	1–19
									FFP	2–5,8–12,16,17
									PRED	8–19
16	4/17/96	5/4/96	18	227	112	7	2,072	428	CYA	1–18
									FFP	1–17
									PRED	7–18
									EX	12,14
17	12/3/96	12/6/96	4	213	83	10	1,793	181	CYA	1–4
									PRED	1–4
									FFP	1–4
									EX	2
18	5/20/97	6/4/97	15	165	53	166	353	139	CYA	1–15
Mean ±SE			31 ± 8	335 ± 44	156 ± 37	42 ± 9	1,085 ± 123	372 ± 60		

*Platelet count is · 10^9/L, LDH is IU/L, Retic is · 10^9/L. Remission platelets are 405 ± 8 · 10^9/L platelets (n = 240), LDH 261 ± 6 IU/L (n = 175), and reticulocytes 120 ± 6 · 10^9/L (n = 125). PRED = prednisone, EX = plasma exchange, FFP = fresh frozen plasma, VCR = vincristine, SPL = splenectomy, CYA = cyclosporine.

[a]Numbers indicate the days on which therapy was given. Therapy is only shown up to episode resolution. For episode 1, prednisone, plasma exchange, and FFP were not given on every day in the range.

TABLE II. Comparison of Various Parameters (Mean ± SE) of TTP Relapses Treated With Vs. Without Cyclosporine[†]

	Episodes 2–7 (no cyclosporine)	Episodes 8–18 (cyclosporine used)	Episodes 2–18 (all relapses)
Episode duration (days)	30 ± 12 (6)	22 ± 4 (11)	25 ± 5 (17)
Lowest platelets ($\cdot 10^9$/L)	39 ± 4 (6)	47 ± 14 (11)	44 ± 9 (17)
Peak LDH (IU/L)	836 ± 47 (6)	1,053 ± 172 (11)	976 ± 141 (17)
Peak Retic ($\cdot 10^9$/L)	348 ± 42 (5)	302 ± 34 (11)	316 ± 27 (16)
Drop in HCT (%)	10.3 ± 1.4 (6)	8.5 ± 1.7 (11)	9.1 ± 1.2 (17)
Days since last episode	411 ± 71 (6)	293 ± 51 (11)	335 ± 42 (17)
Days since last therapy	194 ± 71 (6)	134 ± 41 (11)	155 ± 36 (17)
Days to stop prednisone after episode resolution	197 ± 28 (6)*	78 ± 25 (11)[a],**	120 ± 23 (17)[a]
Days to stop cyclosporine after episode resolution		113 ± 15 (10)*	113 ± 15 (10)

[†]Values in parentheses = number of relapses in analysis. Days since last episode = number of days since resolution of previous episode to diagnosis of relapse. Days since last therapy = number of days from discontinuation of maintenance therapy to diagnosis of relapse.
[a]Includes 4 episodes not treated with prednisone.
*Also indicates total duration of maintenance therapy ($P = 0.011$).
**$P = 0.005$, 1-tailed t-test, compared with days to stop prednisone = no cyclosporine.

$<2.5 \cdot$ baseline, which occurred during most treatment courses. However, improvement in the creatinine level occurred following all episodes even while the patient continued to receive maintenance cyclosporine.

DISCUSSION

This patient had 18 clinically distinct episodes of TTP over 18 years. To our knowledge, this is the highest number of episodes reported in a single patient. No clearly recognizable precipitating factors for the relapses were identified. However, for about 1 week prior to the diagnosis of many of the episodes he experienced vague ''flu-like'' symptoms including myalgias, nasal congestion, and hot and cold spells. Whether these symptoms indicated early features of TTP relapse or a viral syndrome is not clear.

Response of 11 episodes in this patient and 10 episodes in 8 others [6–10] to cyclosporine-containing regimens suggests that cyclosporine is an effective drug for treatment of TTP. In the 8 other individuals reported in the literature, cyclosporine was used as salvage therapy in 6. Five had not responded to plasma exchange with or without other therapies, and 1 relapsed during steroid taper. Cyclosporine was used in conjunction with steroids in 3. Response was noted in all cases in 1 to 8 days. Similar to our patient, 2 individuals relapsed 1 to 3 months after cyclosporine was stopped. Both responded to re-institution of the drug. Cyclosporine alone was also used successfully as primary therapy in 2 patients who developed TTP after autologous bone marrow transplantation. At the time of initiation of treatment with cyclosporine, platelets were $\geqslant$24,000/μL in 7 individuals and $<$20,000/μL in 1.

We first used cyclosporine for our patient's eighth episode that failed to respond to FFP and prednisone. Subsequently, we used it as a first line agent to avoid or minimize the use of prednisone, which caused difficulty with his diabetic control. With cyclosporine we completely avoided prednisone in 4 relapses, and significantly decreased the duration of maintenance prednisone as well as the total duration of maintenance therapy received after achieving remission. However, cyclosporine ± FFP alone was only effective in 4 milder TTP relapses. The composite data suggest that cyclosporine alone is effective therapy for ''milder'' episodes of TTP, and can be an important adjunct to other therapies in more severe and/or refractory episodes.

We did not use plasma exchange to treat episodes 2–15 since the patient did not have severe thrombocytopenia, renal failure, or neurological changes. Also, the initial episode failed to respond to extensive plasma exchange and only remitted following splenectomy while continuing prednisone ± FFP. In episodes 16 and 17, the patient had severe thrombocytopenia, which responded rapidly to plasma exchange. Whether the concurrent use of cyclosporine and prednisone facilitated the rapid response to plasma exchange and/or maintenance of the response is unknown.

Each of the treatment modalities used in this patient have immunosuppressive and/or immunomodulatory effects. Splenectomy removes cells involved in many aspects of immune function. FFP inhibits the proliferative response of lymphocytes [11]. Glucocorticoids inhibit interleukin (IL)-1, IL-2, IL-6, IL-8, and TNF-α production [12–14]. They also inhibit the proliferation stimulatory effect of IL-2 on T cells by interfering with signal transduction mediated through the IL-2 receptor (IL-2R) [15]. Cyclosporine's predominant effect on T cells is inhibition of IL-2R expression and blockade of IL-2 production [16]. While the mechanism of action of cyclosporine and prednisone in induction of TTP remission is not

known, it is likely due to immunosuppressive and/or immunomodulatory effects.

Possible toxicity of cyclosporine observed in this patient was one episode of localized Herpes zoster infection, and renal insufficiency. Acute elevation of creatinine was observed at the times of TTP relapse prior to (re)-institution of cyclosporine therapy. Progressive elevation in creatinine occurred during relapses while on cyclosporine. However, improvement in renal function occurred following resolution of all relapses prior to dose reduction or discontinuation of cyclosporine. Thus, we believe that the predominant cause of the mild to moderate renal insufficiency observed in our patient was TTP.

Cyclosporine has been associated with the development of a TTP-like syndrome predominantly in individuals after bone marrow, renal, liver, or heart transplantation [17,18]. The incidence after bone marrow transplantation is 7–28%, and is not known following other transplants. Cyclosporine administration is considered to be associated with endothelial damage, which may be the inciting event, and has also been shown to decrease prostacyclin generation in endothelial cell cultures [18]. Cyclosporine-associated TTP usually responds to discontinuation of cyclosporine with or without concurrent plasma exchange, plasma infusion, steroid therapy, and/or IV-Ig infusion. However, some cases have cleared with plasma exchange while continuing to administer cyclosporine, suggesting that cyclosporine alone may not be sufficient to induce the syndrome.

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