Treatment of Severe Immune Thrombocytopenia Associated with Systemic Lupus Erythematosus: 59 Cases

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ABSTRACT. ***Objective***. To evaluate the response to treatment in a large cohort of patients with systemic lupus erythematosus (SLE) associated with autoimmune thrombocytopenia.

Methods. Response to treatment was assessed retrospectively in 59 patients with SLE, either definite (n = 44) or incomplete (n = 15), associated with frank autoimmune thrombocytopenia (defined as platelet count $< 50 \times 10^9$/l). Response to treatment was classified as complete (CR: platelet count $> 150 \times 10^9$/l), partial (PR: platelet count $> 50 \times 10^9$/l), or failure (FR) in the other cases.

Results. Oral prednisone alone was used in 50 of the 59 patients (mean initial dose 1 mg/kg body weight/day). A response was obtained in 80% of cases (CR in 28, PR in 12) but only 11 (22%) had a sustained response (CR, n = 7; PR, n = 4). In contrast, combined treatment with prednisone and either danazol (n = 18) or hydroxychloroquine (n = 11) resulted in 50% (7 CR, 2 PR) and 64% (4 CR, 3 PR) longterm responses, respectively, allowing prednisone to be withdrawn or the dose tapered below 0.2 mg/kg body weight/day. High dose methylprednisolone pulses (n = 10) and intravenous immunoglobulin (IVIG) (n = 31) resulted in positive responses in 60% (4 CR, 2 PR) and 65% (12 CR, 8 PR) of cases, respectively, but the response was transient in each case. Splenectomy (n = 17) resulted in 65% longterm responses (10 CR, 1 PR). Only 2 longterm partial responses were obtained with the 22 immunosuppressant-containing regimens administered to 14 patients. At the end of the study, a response was observed in 52 (88%) patients [CR: 36 (61%), PR: 16 (27%)], mainly as a result of splenectomy or combined treatment with prednisone and either danazol or hydroxychloroquine.

Conclusion. Longterm remission was obtained in the majority of patients. The major treatments inducing remission were splenectomy and prednisone combined with danazol or hydroxychloroquine. (J Rheumatol 2002;29:75–83)

Key Indexing Terms:
AUTOIMMUNE THROMBOCYTOPENIA CORTICOSTEROID DANAZOL HYDROXYCHLOROQUINE SPLENECTOMY SYSTEMIC LUPUS ERYTHEMATOSUS

Immune thrombocytopenia frequently complicates systemic lupus erythematosus (SLE) and may be severe with a low platelet count ($< 50 \times 10^9$/l) in 5 to 10% of patients[1-5]. Although the association of immune thrombocytopenia with SLE is well known, the literature is based mainly on small series of patients or on isolated case reports[2]. Thus, no established standard therapy for immune thrombocytopenia with SLE has been recognized. For example, corticosteroids are usually considered the first-line treatment, but the longterm response to this treatment is unknown and a relapse of thrombocytopenia is frequently observed if steroid dose is tapered. Intravenous immunoglobulins (IVIG) and high dose methylprednisolone pulses (HDMP) have also been reported as effective but only in small series[6,7]. Cytotoxic agents have been evaluated in retrospective studies including only a small number of patients[8,9]. Finally, the extent to which splenectomy cures SLE associated thrombocytopenia is unclear and this procedure is considered by some authors to be contraindicated in SLE[10,11].

We evaluated the response to treatment in a large cohort of patients in whom severe thrombocytopenia was the leading manifestation of SLE.

MATERIALS AND METHODS

Outcome and response to treatment were assessed retrospectively in patients with SLE, either definite [≥ 4 1982 American Rheumatism

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Association criteria (ARA)[12]] or incomplete (ARA criteria, n = 3), associated with frank autoimmune thrombocytopenia (defined as platelet count < 50×10^9/l on at least 2 consecutive occasions). Patients were included if thrombocytopenia was the leading manifestation of SLE in which extrahematological SLE flare was mild or absent at diagnosis of thrombocytopenia. Five French units participated in this study and all patients who had been followed in these units over a 10 year period and who fulfilled the inclusion criteria were included. SLE activity was assessed using the SLE Disease Activity Index (SLEDAI) score[13].

Immune thrombocytopenia was diagnosed according to standard criteria[14]: thrombocytopenia with normal or high megakaryocyte count in an otherwise normal bone marrow aspirate, no disease other than SLE known to be associated with immune thrombocytopenia [e.g., human immunodeficiency virus (HIV) infection, lymphoproliferative disorders, thyroid and liver diseases] and no treatment with drugs known to induce thrombocytopenia. Patients for whom there was evidence that thrombotic thrombocytopenic purpura[15] was responsible for the low platelet count at disease onset were not included.

Responses to treatment were classified as complete (CR) if the number of platelets increased to above 150×10^9/l and as partial (PR) if the number of platelets increased between 50×10^9/l and 150×10^9/l and reached the initial count at least twice. Treatment was considered a failure (FR) in all other cases.

Statistical analysis. Results are expressed as mean ± 1 standard deviation or as percentages. Lines of treatment were considered for analysis. Comparisons were made using chi-square test (or Fisher's exact test when necessary) for categorical data and nonparametric Kruskal-Wallis analysis of variance for quantitative data. In case of statistical difference between all groups, multiple pairwise comparisons were performed with a t level taking into account the number of comparisons (BMDP statistical software, program 3S).

RESULTS

Patients. Eighty-three patients with SLE and thrombocytopenia were followed in the 5 units during the period of the study. Twenty-four of these patients were not included. Sixteen thrombocytopenic SLE patients were not analyzed for the following reasons: HIV infection (n = 2), drug induced thrombocytopenia (n = 5), insufficient data or patients not regularly followed in the centers participating in the study (n = 9). Eight other patients were not included because thrombocytopenia occurred in association with a severe extrahematological SLE flare manifested mainly as specific fever (n = 4), kidney involvement (n = 4), and central nervous system involvement and myocarditis (n = 2).

Fifty-nine patients [male, n = 10 (17%), female, n = 49 (83%)] with a mean age at SLE diagnosis of 29 ± 12 years (range 13–85) were included. Fifty-five patients (93%) were of Caucasian origin, 3 patients were Afro-Caribbean, and one patient was Asian. Forty-four (75%) of the 59 included patients had definite SLE (mean number of ARA criteria 5.2 ± 1.5) and 15 patients (25%) had incomplete SLE (3 criteria with at least one clinical sign from the ARA criteria in 9 patients). Four of these 15 patients fulfilled the SLE diagnosis according to the revised criteria for ARA classification[16]. The main characteristics of the 15 patients with incomplete SLE are summarized in Table 1.

Thrombocytopenia was the presenting feature of SLE in 43 of the 59 patients (73%), whereas it occurred after a mean duration of SLE of 77 months in the other 16 patients (27%). The mean platelet count at diagnosis of thrombocytopenia was 20 ± 17 × 10^9/l (range 1–49). One or several sites of SLE visceral involvement were diagnosed in 20 patients (34%) during the followup period. There was a history of prior visceral involvement in 6 patients (kidney involvement, n = 5; pleurisy and pericarditis, n = 2; lupus pneumonitis, n = 1) at diagnosis of thrombocytopenia, but thrombocytopenia was the leading manifestation of SLE. Fourteen other patients experienced visceral involvement during followup (kidney involvement, n = 6; neurologic manifestations, n = 5; pleurisy and pericarditis, n = 4; lupus pneumonitis, n = 1). The mean SLEDAI score at diagnosis of thrombocytopenia was 4 ± 4. The mean period of followup from date of diagnosis of SLE-associated thrombocytopenia was 74 ± 70 months (range 6-384).

Response to Treatment

Oral prednisone alone. Oral prednisone (mean dose of 1 mg/kg body weight/day) was used as the first-line treatment in 57 patients (97%). However, response to oral prednisone could not be evaluated in 7 patients because another treatment was quickly added (n = 6) or the followup period was too short (< 2 mo) (n = 1). Thus, the analysis of the response to oral prednisone alone only included 50 patients.

An initial response was observed in 40 patients (80%) with a CR in 28 patients (56%) and a PR in 12 (24%) (Table 2). A sustained response to prednisone alone was observed in 11 patients (22%) (CR n = 7; PR n = 4), with a mean followup period of 78 ± 63 months (Table 2 and 3). The mean initial dose of prednisone was 1 ± 0.2 mg/kg body weight (bw)/day and the mean duration of treatment with corticosteroids alone in longterm responders was 23 ± 24 months (range 1-70). At the end of the study, 1 responder was still being treated with a high dose of prednisone (0.5 mg/kg bw/day); 2 patients received a low dose (0.1 and 0.07 mg/kg bw/day, respectively) and 8 patients were free of treatment. For these 8 patients, the mean duration of treatment with corticosteroids was 13 ± 14 months and the mean duration of followup after withdrawal of corticosteroids was 77 ± 61 months.

Oral prednisone did not induce a longterm response in 39 (78%) patients. Fifteen (30%) patients were resistant to oral prednisone at a dose of 1 (n = 13) or 2 mg/kg bw/day (n = 2). Twenty-one (42%) patients initially responded to oral prednisone but relapsed while still receiving high dose prednisone (mean 0.7 ± 0.3 mg/kg bw/day, range 0.2-1). Three patients classified as longterm responders initially had a sustained response to oral prednisone but thrombocytopenia relapsed 4, 16, and 48 months, respectively, after withdrawal of oral prednisone.

IVIG. IVIG was given at a dose of 2 g/kg bw for 2 to 5 days in 31 patients. A transient response was observed in 20 patients (65%) [CR 12 (39%); PR 8 (26%)]. Mean delay

Table 1. Characteristics of the patients with incomplete SLE.

Pt	ANA Titer	Clinical Manifestation (ARA Classification)	Laboratory Manifestation (ARA Classification)†	Other Clinical Manifestation Related to SLE	Other Biological Signs Related to SLE	No. of Criteria (Revised SLE Classification)[16]
1	1/2560	Malar rash	Leukopenia, lymphopenia	—	LAC, low C3 level	4
2	1/2560	Malar rash	—	—	Low C4 level	3
3	1/200	Photosensitivity	—	Alopecia, sicca syndrome	LAC, aCL, low C4 level	4
4	1/320	Malar rash	Lymphopenia		Low C3 and C4 levels	3
5	1/640	Neurologic involvement		—	—	3
6	1/1280	Arthritis	—	—	LAC, aCL	4
7	1	Arthritis	—	—	Low C3 and C4 levels	3
8	1/160	Discoid rash	—	RP, alopecia sicca syndrome, livedo	LAC, low C4 level	4
9	1/640	Photosensitivity	—	RP	—	3
10	1/640	—	VDRL+	RP, deep vein thrombosis	LAC, aCL, low C3 level	3
11	1/320	—	VDRL +	Lymphadenopathy	LAC, aCL	3
12	1/800	—	VDRL +, lymphopenia	Deep vein thrombosis	LAC, Anti-Ro (SSA), low C4 level	3
13	1/2560	—	VDRL +, lymphopenia	—	LAC, aCL	3
14	1/320	—	Proteinuria, leukopenia, lymphopenia	Arthralgias (without arthritis)	Anti-Ro (SSA)	3
15	1/2560	—	Anti-Sm, lymphopenia	—	Anti-Ro (SSA), anti-SSB, low C4 level	3

† Except thrombocytopenia.
aCL: anticardiolipin antibody; ANA: antinuclear antibody; LAC: lupus anticoagulant; RP: Raynaud's phenomenon.

Table 2. Initial and longterm response to oral prednisone alone, high dose methylprednisolone (HDMP), and intravenous immunoglobulin (IVIG).

	Initial	Response (%)	Longterm	Response (%)
Oral prednisone, n = 50	CR: 28 (56) PR: 12 (24) Failure: 10 (20)	80%	CR: 7 (14) PR: 4 (8) Failure: 39 (78)	22%
HDMP, n = 10	CR: 4 (40) PR: 2 (20) Failure: 4 (40)	60%	CR: 0 (0) PR: 0 (0) Failure: 10 (100)	0%
IVIG, n = 31	CR: 12 (39) PR: 8 (26) Failure: 11 (35)	65%	CR 0 (0) PR: 0 (0) Failure: 31 (100)	0%

CR: complete response; IVIG: intravenous immunoglobulin; HDMP: high dose methylprednisolone; PR: partial response.

after IVIG infusion until a platelet count ≥ 50×10^9/l was achieved was 4.6 ± 2.8 days. No sustained response was observed, even in the 4 patients treated with repeated IVIG infusions (3 to 12 infusions) (Table 2).

High dose methylprednisolone (HDMP). HDMP was administered at a mean dose of 15 mg/kg bw/day to 10 patients and a transient response was achieved in 6 [CR 4 (40%); PR 2 (20%)]. The mean delay after HDMP infusion until a platelet count ≥ 50×10^9/l was achieved was 7.2 ± 8.8 days. No sustained response was observed, even in the 2 patients who received monthly HDMP infusions (4 and 5 infusions, respectively) (Table 2).

Danazol and oral prednisone. Eighteen patients received danazol at a dose of 600 mg/day (n = 10), 400 mg/day (n = 2) or 50 mg/day (n = 6) (Table 4). In all cases, danazol was added to oral prednisone at a mean dose of 0.7 mg/kg bw/day after failure of prednisone alone. Twelve patients had received another treatment, without a sustained response, before danazol was given (IVIG n = 7; immunosuppressants n = 6; hydroxychloroquine n = 4; HDMP n = 3; splenectomy n = 1). A sustained longterm response was observed with combined prednisone and danazol treatment in 9 patients (50%) [CR 7 (39%); PR 2 (11%)] with a mean duration of followup of 28 ± 30 months. This made it

Table 3. Characteristics of patients with a sustained response to prednisone (PRDN) treatment (n = 11).

Pt	ARA Criteria, (no.)	Visceral Involvement Related to SLE*	Duration of Thrombo-cytopenia Before PRDN (mo)	Platelet Count Before PRDN (10^9/l)	Initial Dose of PRDN (mg/kg bw/day)	Duration of PRDN (mo)	Followup (mo)	Longterm Response to PRDN†	Dose of PRDN at the Study Endpoint (mg/kg bw/day)	Followup after PRDN Withdrawal (mo)
1	4	–	0	2	1	1	30	CR	0	29
2	6	–	0	40	0.5	15	68	CR	0	53
3	6	+	0	10	1	12	204	CR	0	192
4	4	–	0	20	1	8	107	CR	0	99
5	6	+	0	49	1	44	180	CR	0	136
6	4	–	0	8	1	18	68	CR	0	50
7	5	+	0	16	1	58	58	CR	0.1	—
8	5	–	4	27	1.5	3	45	PR (70)	0	42
9	3	–	0	26	1	1	12	PR (130)	0	12
10	5	+	168	41	1	18	18	PR (125)	0.5	—
11	4	+	0	9	1	70	70	PR (128)	0.07	—

* Visceral involvement was already present at diagnosis of thrombocytopenia or appeared during followup of the study. † With platelet count (10^9/l) for partial responders. CR: complete response; PR: partial response; PRDN: prednisone; Pt: patient.

Table 4. Characteristics of the patients treated with danazol (n = 18).

Pt	ARA Criteria (No.)	Visceral Involvement Related to SLE*	Duration of Thrombo-cytopenia Before DNZ (mo)	Prior Treatment	Platelet Count Before DNZ (10^9/l)	Dose of DNZ (mg/day)	Treatment with DNZ (dose/day)	Duration of DNZ (mo)	Longterm Response to DNZ†	Treatment at the Study Endpoint	Followup after DNZ Withdrawal (mo)
1	6	–	24	PRDN	25	50	PRDN (0.5 mg/kg)	15	CR	DNZ (50 mg) + PRDN (0.13 mg/kg)	—
2	7	+	15	PRDN, CPM HDMP	29	600	PRDN (0.22mg/kg) + HCQ (400 mg)	13	CR	DNZ (400 mg) + PRDN (0.19 mg/kg) + HCQ (400 mg)	—
3	3	–	3	PRDN, IVIG	8	400	PRDN (1 mg/kg)	13	CR	—	8
4	3	–	0.5	PRDN	5	600	PRDN (1 mg/ kg)	11	CR	—	4
5	3	–	9	PRDN, IVIG VBL, HCQ	66	600	PRDN (0.2 mg/kg) + HCQ (600 mg)	45	CR	HCQ (600 mg)	61
6	4	–	6	PRDN	12	50	PRDN (0.3 mg/kg)	21	CR	DNZ (50 mg) + PRDN (0.08 mg/kg)	—
7	3	–	12	PRDN, IVIG, HCQ	6	400	PRDN (1 mg/ kg)	18	CR	DNZ (300 mg)	—
8	4	–	3	PRDN	3	600	PRDN (1 mg/ kg) + HCQ (600 mg)	8	PR (138)	DNZ (600 mg) + PRDN (0.07 mg/kg)	—
9	4	–	10	PRDN, IVIG	21	50	PRDN (0.7 mg/kg)	34	PR (130)	DNZ (50 mg) + PRDN (0.7 mg/kg)	—
10	4	+	56	PRDN, IVIG, AZA	25	50	PRDN (0.4 mg/kg)	5	Failure	DNZ (50 mg) + PRDN (0.5 mg/kg)	—
11	10	+	37	PRDN, HDMP, CPM	29	600	PRDN (0.2 mg/kg) + HCQ (400 mg)	33	Failure	VBL	—
12	3	–	9	PRDN, IVIG, HCQ	8	600	PRDN (1 mg/kg) + HCQ (600 mg)	22	Failure	Death (TTP)	—
13	10	+	0	PRDN	42	600	PRDN (2 mg/kg)	4	Failure (hepatitis)	PRDN	—
14	4	+	145	PRDN, HCQ	25	600	PRDN (0.15) + HCQ (400 mg)	2	Failure (hepatitis)	SPLN	—
15	3	–	12	PRDN	30	600	PRDN (1 mg/kg)	4	Failure	PRDN	—
16	6	–	61	PRDN, SPLN, VCR, IVIG	9	600	PRDN (0.5 mg/ kg)	1	Failure (rash)	HCQ	—
17	5	+	41	PRDN, HDMP	4	50	PRDN (0.4 mg/kg)	5	Failure	PRDN + HCQ + VBL	—
18	4	+	38	PRDN, IFN	45	50	PRDN (0.45 mg/kg)	29	Failure	PRDN + CPM	—

* Visceral involvement was already present at diagnosis of thrombocytopenia or appeared during the followup of the study. †With platelet count (10^9/l) for PR. AZA: azathioprine; CPM: cyclophosphamide; CR: complete response; DNZ: danazol; HCQ: hydroxychloroquine; HDMP: high dose methylprednisolone, IFN: interferon-α ; IVIG: intravenous immunoglobulin; PR: partial response; PRDN: prednisone; Pt: patient; SPLN: splenectomy; VBL: vinblastine; VCR: vincristine; TTP: thrombotic thrombocytopenic purpura.

possible to withdraw prednisone (n = 4) or taper the dose below 0.2 mg/kg bw/day (n = 5). The mean duration of danazol treatment for the 9 responders was 20 ± 12 months. At the end of the study, 6 responders were still being treated with danazol after a mean duration of treatment of 18 ± 9 months. Three responders who had been treated with danazol for a mean duration of 23 ± 19 months were free of treatment with a mean duration of followup of 24 ± 32 months after withdrawal of danazol. Danazol did not induce a longterm response in 9 (50%) patients, including 3 in whom prednisone was withdrawn due to the occurrence of a side effect (Table 4).

Hydroxychloroquine and oral prednisone. In 11 patients, hydroxychloroquine (mean dose 400 mg/day) was used to treat thrombocytopenia (Table 5). Hydroxychloroquine was given with oral prednisone, at a mean dose of 0.7 mg/kg bw/day, to 10 patients after prednisone alone had failed. Seven patients had previously received other treatments without longterm success (IVIG n = 5; immunosuppressants n = 2; HDMP n = 2; danazol added to prednisone n = 1; splenectomy n = 1). A sustained longterm response was observed with combined prednisone and hydroxychloroquine treatment in 7 patients (64%) [CR 4 (36%); PR 3 (27%)] with a mean duration followup of 31 ± 16 months, which made it possible to taper the dose of prednisone below 0.2 mg/kg bw/day. The mean duration of treatment with hydroxychloroquine in the responders was 31 ± 17 months. All responders were still being treated with hydroxychloroquine at the end of the study.

Immunosuppressants. Fourteen patients received one or several immunosuppressants for thrombocytopenia (Table 6). In two of these patients, thrombocytopenia was associated with severe extrahematological SLE. Nine patients received only one immunosuppressant, 4 received 2 in succession, and one patient received 5 different immunosuppressants. A total of 22 periods of treatment were observed. The mean duration of treatment with immunosuppressants was 8 ± 11 months. A transient response was observed in 7 of the 22 (32%) treatment periods [CR 3 (14%), PR 4 (18%)]. One patient who received repeated infusions of vinblastine over an 18 month period had a partial sustained response, which persisted 7 months after the end of vinblastine treatment. Another patient was still being treated with vinblastine infusions at the end of the study and had a sustained partial response with 25 months of followup. Longterm failure was observed in the other 12 (86%) patients.

Splenectomy. Seventeen patients (definite SLE n = 12; incomplete SLE n = 5) underwent splenectomy after a mean duration of thrombocytopenia of 30 ± 36 months (Table 7).

Table 5. Characteristics of the patients treated with hydroxychloroquine (n = 11).

Pt	ARA Criteria (No.)	Visceral Involvement Related to SLE*	Duration of Thrombocytopenia Before HCQ (mo)	Prior Treatment	Platelet Count Before HCQ (10^9/l)	Dose of HCQ (mg/day)	Treatment Associated with HCQ (dose/day)	Duration of Treatment with HCQ (mo)	Longterm Response to HCQ†	Treatment at Study Endpoint
1	5	+	142	PRDN	125	400	PRDN (0.5 mg/kg)	14	CR	HCQ (400mg) + PRDN (0.15 mg/kg)
2	5	–	2	PRDN, IVIG	120	400	PRDN (1 mg/kg)	36	CR	HCQ (400 mg) + PRDN (0.1 mg/kg)
3	4	–	40	PRDN	30	400	PRDN (0.65 mg/kg)	63	CR	HCQ (400 mg) + PRDN (0.2 mg/kg)
4	4	–	7	PRDN, HDMP	41	400	PRDN (0.9 mg/kg)	18	CR	HCQ (400 mg) + PRDN (0.18 mg/kg)
5	5	–	72	PRDN	41	400	PRDN (0.75 mg/kg)	37	PR (140)	HCQ (400 mg) + PRDN (0.13 mg/kg)
6	3	–	5	PRDN, HDMP	28	400	PRDN (1 mg/kg)	17	PR (60)	HCQ (400 mg) + PRDN (0.05 mg/kg)
7	5	–	14	PRDN, IVIG	50	400	—	31	PR (130)	HCQ (400 mg)
8	3	–	3	PRDN, IVIG VBL	25	600	PRDN (0.5 mg/kg)	6	Failure	HCQ (600 mg) + PRDN (0.07 mg/kg)
9	4	+	48	PRDN	100	400	PRDN (0.35 mg/kg)	91	Failure	IVIG, DNZ
10	6	–	48	PRDN, SPLN, VCR, IVIG CPM, DNZ	9	400	PRDN (0.3 mg/kg)	3	Failure	HCQ (400 mg)
11	3	–	0.5	PRDN, IVIG	6	400	PRDN (1 mg/kg)	11	Failure	DNZ (300 mg)

* Visceral involvement was already present at diagnosis of thrombocytopenia or appeared during followup of the study.
†With platelet count (10^9/l) for PR.
CPM: cyclophosphamide; CR: complete response; DNZ: danazol; HCQ hydroxychloroquine; HDMP: high-dose methylprednisolone; IVIG: intravenous immunoglobulin; PR: partial response; PRDN: prednisone; SPLN: splenectomy; VBL: vinblastine; VCR: vincristine.

Table 6. Characteristics of the patients treated with immunosuppressive (IS) drugs (n = 14).

Pt	ARA Criteria (No.)	Visceral Involvement Related to SLE*	Duration of Thrombocytopenia Before IS (mo)	Prior Treatment Before IS	IS	Platelet Count (10^9/l) Before IS	Duration of IS Treatment (mo)	Longterm Response to IS†
1	4	–	4	PRDN, IVIG, HDMP, dapsone	VBL	4	10	PR (70)
2	3	–	24	PRDN, IVIG, SPLN	VBL	30	18	PR (71)
3	3	–	3	PRDN, IVIG	VBL	3	1	Failure
4	10	+	8	PRDN, HDMP	CPM	29	24	Failure
5	7	+	2	PRDN, HDMP, IVIG	CPM	48	10	Failure
6	10	+	2	PRDN	CPM	42	7	Failure
7	3	–	2	PRDN, IVIG	VBL	30	4	Failure
8	6	–	48	PRDN, SPLN	VCR	7	2	Failure
			54		CPM	9	7	Failure
			101		VBL	6	2	Failure
			102		AZA	7	3	Failure
			156		Cyclo	9	4	Failure
9	5	+	67	PRDN, HDMP, DNZ	VBL	46	7	Failure
10	4	–	6	PRDN, IVIG	AZA	44	52	Failure
11	5	+	2	PRDN	AZA	30	2	Failure
			2		Cyclo	25	2	Failure
12	4	+	12	PRDN	IFN	30	6	Failure
			65		Cyclo	3	7	Failure
13	6	+	3	PRDN	CPM	3	6	Failure
			73		Cyclo	3	7	Failure
14	5	+	23	PRDN, HDMP, IVIG, SPLN	CPM	32	3	Failure
			26		VCR	28	1	Failure

* Visceral involvement was already present at diagnosis of thrombocytopenia or appeared during the followup of the study. †With platelet count (10^9/l) for PR. AZA: azathioprine; Cyclo: cyclosporine; CPM: cyclophosphamide; DNZ: danazol; HCQ: hydroxychloroquine; HDMP: high dose methylprednisolone; IFN interferon-α; IS: immunosuppressants; IVIG: intravenous immunoglobulin; PR: partial response; PRDN: prednisone; Pt: patient; SPLN: splenectomy; VBL: vinblastine: VCR: vincristine.

Table 7. Characteristics of the patients who underwent splenectomy (SPLN) (n = 18).

Pt	ARA Criteria (No.)	Visceral Involvement Related to SLE*	Duration of Thrombocytopenia Before SPLN (mo)	Prior Treatment Before SPLN	Platelet Count (10^9/l) Before SPLN	Longterm Response to SPLN †	Followup after SPLN (mo)
1	4	+	28	PRDN	36	CR	9
2	4	–	8	PRDN, IVIG	47	CR	42
3	3	–	8	PRDN, IVIG	4	CR	9
4	4	–	26	PRDN, IVIG	1	CR	13
5	4	–	42	PRDN, DNZ, HCQ, Dapsone	30	CR	11
6	3	+	35	PRDN, HCQ, Dapsone	35	CR	6
7	3	–	28	PRDN, DNZ, IVIG	8	CR	80
8	4	+	14	PRDN	4	CR	370
9	9	+	14	PRDN, IVIG	4	CR	125
10	7	+	20	PRDN, IVIG	25	CR	16
11	4	+	150	PRDN, HCQ, DNZ, IVIG	3	PR (88)	24
12	5	+	2	PRDN, AZA, Cyclo	10	Failure	31
13	5	+	2	PRDN, HDMP, IVIG	38	Failure	3
14	3	–	5	PRDN, IVIG, VBL	19	Failure	78
15	3	–	50	PRDN, IVIG	1	Failure	47
16	6	–	9	PRDN	35	Failure	209
17	5	+	74	PRDN, HDMP, DNZ, VBL, IVIG	18	Failure	31
18	4	–	SPLN before thrombocytopenia	—	—	Failure	—

† With platelet count (10^9/l) for PR.
*Visceral involvement was already present at diagnosis of thrombocytopenia or appeared during the followup of the study.
AZA: azathioprine; Cyclo: cyclosporine; DNZ: danazol; HCQ: hydroxychloroquine; HDMP: high dose methylprednisolone; IVIG: intravenous immunoglobulin; PR: partial response; PRDN: prednisone: Pt: patient; SPLN: splenectomy: VBL: vinblastine.

Table 8. Patient characteristics and longterm response (PR and CR) in all treatment groups.

Treatments	No. of Pts	Mean No. of ARA Criteria	No. of Pts with Incomplete SLE (%)	No. of Pts with Visceral Involvement Related to SLE (%)*	Median Duration of Thrombocytopenia Before Treatment (mo)	Mean Platelet Count Before Treatment (10^9/l)	No. of Longterm (PR or CR) Responders (%)	Percentage of Longterm Responders Among Pts with Incomplete SLE	Percentage of Longterm Responders Among Pts with Definite SLE	p Value‡
Oral prednisone alone	50	4.5 ± 1.5	11 (22%)	16 (32%)	0	17 ± 15	11/50 (22%)	9 %	25%	0.23
HDMP	10	5.8 ± 2.5	2 (20%)	8 (80%)	1	25 ± 14	0 (0%)	0 (0%)	0 (0%)	1
IVIG	31	4.6 ± 1.8	10 (32%)	11 (35%)	1	13 ± 12	0 (0%)	0 (0%)	0 (0%)	1
Danazol	18	4.8 ± 2.2	6 (33%)	7 (39%)	12	22 ± 17	9 (50%)	67%	41%	0.31
HCQ	11	4.3 ± 1	3 (27%)	2 (18%)	14	52 ± 43†	7 (64%)	33%	75%	0.28
IS	14	5.4 ± 2.3	3 (21%)	8 (57%)	18	21 ± 16	2 (14%)	33%	9%	0.38
Splenectomy	18	4.5 ± 1.5	5 (28%)	9 (50%)	17	19 ± 16	11 (61%)	60%	62%	0.68

* Visceral involvement related to SLE was present at the time of thrombocytopenia or appeared during followup.

† Mean platelet count in the HCQ patient group was significantly higher versus all others (P = 0.01). No difference was observed for other criteria except median duration of thrombocytopenia before treatment.

‡ Comparison of percentage of longterm responders, patients with incomplete SLE versus definite SLE for each treatment.

CR: complete response; HCQ: hydroxychloroquine; HDMP: high dose methylprednisolone; IS: immunosuppressive drugs; IVIG: intravenous immunoglobulin; PR: partial response.

One patient who underwent successful splenectomy for isolated autoimmune hemolytic anemia 64 months before onset of thrombocytopenia was not included in the analysis. The mean platelet count before splenectomy was 19 ± 16 × 10^9/L. A sustained response was observed in 11 (65%) patients [CR 10 (59%); PR 1 (6%)] with a mean followup period of 64 ± 108 months.

SLE flare occurred 33 ± 22 months after splenectomy in 7 of 18 (39%) patients. This incidence was not significantly different from that observed in nonsplenectomized patients [11/41 (27%), P = 0.4] during similar followup periods (65 ± 93 mo for splenectomized patients vs 68 ± 57 mo for nonsplenectomized patients). In 3 patients, SLE flare occurred < 6 months after splenectomy (3, 3, and 5 mo, respectively). It was limited to transient and benign rheumatological/cutaneous signs in two. In contrast, the third died of fulminant thrombotic thrombocytopenic purpura associated with *Staphylococcus aureus* pneumonia whereas no sign of thrombotic microangiopathy was observed before splenectomy. No serious infectious complication was observed after splenectomy in the other patients.

Response in all treatment groups. Patient characteristics and percentages of responders to treatments are summarized in Table 8. The mean numbers of ARA criteria and the percentages of patients with incomplete SLE were similar in all the groups. In contrast, the mean platelet count before treatment was higher in the group of patients treated with hydroxychloroquine (P = 0.01). No statistical differences were found between the percentages of responders to treatments in the groups of patients with incomplete SLE and in the groups with true SLE.

To summarize the response to treatment at the end of the study for the entire cohort of patients, 88% (52/59) of the patients were in remission, which was complete in 61% (36/59). The major treatments inducing partial or complete remission were mainly splenectomy (n = 11), prednisone alone (n = 11), prednisone with danazol (n = 9) and prednisone with hydroxychloroquine (n = 7). Only 7 (12%) patients had failed to respond at the end of the study.

DISCUSSION

Conflicting results have been reported concerning the outcome of SLE-associated thrombocytopenia and there is a lack of randomized studies comparing treatments to help clinicians decide on a therapeutic strategy. We describe a large series of patients with severe thrombocytopenia requiring specific regimes. All had either definite or incomplete SLE. Patients with immune thrombocytopenia associated with antinuclear antibodies but no clinical signs suggestive of SLE were excluded because their prognosis and response to treatment are similar to those of patients with isolated idiopathic autoimmune thrombocytopenic purpura (ITP)[17-19].

Corticosteroids were used as the first-line treatment for the majority of patients in our study. An initial response was obtained in 80% of patients, but only 20% had a sustained complete response when corticosteroid dose was tapered, as observed in adult patients with ITP[14]. Thus, our study does not confirm previous results suggesting that, in patients with SLE, platelet count could be maintained in the "safe" range of > 50 × 10^9/l with low dose or sometimes with no corticosteroid therapy[4].

In contrast, we found that combined prednisone and danazol or hydroxychloroquine treatment appears promising

because it was associated with longterm responses in 50% and 64% of cases, making it possible to withdraw prednisone or to taper the dose below 0.2 mg/kg bw/day. Danazol has been reported to be effective for treating immune thrombocytopenia or Evans' syndrome complicating SLE in isolated cases and small series[20-22]. However, further studies are required to determine the optimum dose in terms of tolerance and efficacy and duration of treatment, because relapses appear to be common after withdrawal[21]. Our results suggest that hydroxychloroquine may also be an effective, well tolerated, and inexpensive treatment for immune thrombocytopenia complicating SLE. This effect may be due to an immunomodulatory mechanism[23]. A prospective randomized trial has shown that hydroxychloroquine is effective in preventing SLE flares[24]. The use of this drug as a therapy for severe thrombocytopenia deserves further evaluation in randomized trials because hydroxychloroquine was used in our study mainly in patients with only moderate thrombocytopenia.

Responses to regimens containing immunosuppressants were poor: only 2 sustained partial responses were obtained among the 14 patients treated. This conclusion should be tempered due to the small number of patients treated and the possible biases of our retrospective study. However, although patients treated with immunosuppressants probably had more severe disease, it must be emphasized that a response was observed with hydroxychloroquine or danazol associated with low doses of corticosteroids in some patients who were resistant to immunosuppressants.

IVIG have been reported to be effective in thrombocytopenic SLE patients in case series[6,7]. Our results confirm in a large number of patients that IVIG and HDMP rapidly increase the platelet count above a "safe" cutoff. However, as observed in ITP[25,26], this effect is only transient, even in patients receiving repeated infusions. The short duration of activity, the high cost of IVIG, and the potentially severe side effects of these treatments suggest that their use should be limited to patients refractory to oral prednisone with life threatening complications or requiring surgery (especially splenectomy).

The precise role of splenectomy in the treatment of SLE associated thrombocytopenia remains a matter of debate. Several authors have reported that splenectomy may be less effective in SLE than in autoimmune thrombocytopenic purpura, and that a significantly higher incidence of cutaneous vasculitis and serious infections occur in patients with SLE who have undergone splenectomy[10,11]. Our experience is different because a sustained platelet response was achieved after splenectomy in 61% of our patients and we did not observe an increase in the incidence of SLE flare or severe infectious complications, even after a long period of followup. One splenectomized patient died of fulminant thrombotic thrombocytopenic purpura (TTP) 3 months after splenectomy. There is no evidence, however, that TTP could have been provoked by splenectomy, and it should be stressed that splenectomy has been found to be an effective treatment for preventing relapse of "idiopathic" TTP[27]. Thus our study suggests, in accord with published data[28-30], that SLE does not contraindicate splenectomy. A study with a larger number of patients would be useful to confirm this result.

A response was obtained in the majority of patients. The major treatments leading to partial or complete remission were splenectomy, or prednisone associated with danazol or hydroxychloroquine.

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