Lupus (2003) 12, 52–57
www.lupus-journal.com

PAPER

Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus

JA Aviña-Zubieta[1,2]*, G Galindo-Rodríguez[2], I Robledo[1], J Vela-Ojeda[3], M Vadillo-Buenfil[1], A Rosas-Cabral[1,3] and D Salazar-Exaire[1]

[1]Clinical Epidemiology Research Unit, Hospital de Especialidades Centro Médico Nacional 'La Raza', Instituto Mexicano del Seguro Social, Seris y Zaachila SN, Col. La Raza, México, D.F. 02990, México; [2]Rheumatic Disease Unit, Hospital de Especialidades Centro Médico Nacional 'La Raza'. Instituto Mexicano del Seguro Social, Seris y Zaachila SN, Col. La Raza, México, D.F. 02990, México; and [3]Hematology Department, Hospital de Especialidades Centro Mèdico Nacional 'La Raza', Instituto Mexicano del Seguro Social, Seris y Zaachila SN, Col. La Raza, México, D.F. 02990, México

The purpose of this study was to compare the long-term effectiveness among danazol, corticosteroids, cytotoxics, and dapsone in the treatment of hematological manifestations of systemic lupus erythematosus (SLE). Medical charts of all patients seen at the Rheumatic Disease Unit from January to December of 1998 were reviewed. Patient characteristics, disease and treatment information were collected. The main outcome measures were the cause of and time to discontinuation of drugs used to treat hematological manifestations of SLE resulting from all causes, mainly toxicity and inefficacy or both. Bivariate analysis including one-way ANOVA and χ^2 tests were used to compare differences between means and proportions, respectively. Survival curves among the different drugs were evaluated using the Kaplan–Meier method. Multivariate analysis (Cox-regression) was used to adjust for potential confounders. After all medical records were reviewed 41 cases were eligible. Two cases had hemolytic anemia, 34 had thrombocytopenia, and five had both. These cases had received a total of 121 cycles of treatment at different times and they represent the study population (corticosteroids $n = 37$, danazol $n = 51$, citotoxic drugs $n = 29$, and dapsone $n = 4$). Crude rates of discontinuations due to any cause, toxicity and inefficacy were not statistically significant among the drugs. However, the Kaplan–Meier curves showed statistically significant difference for discontinuations due to all causes as well as inefficacy. Prednisone and cytotoxic drugs had the lowest probability of continuation. In contrast, there were not statistically significant differences among the drugs with respect to first relapse. This is the first study examining the long-term termination rates of several drugs used to treat hematological manifestations of SLE. Using rates of discontinuation adjusted for time there were statistically significant differences among the drugs. Danazol had the highest probability of continuation. *Lupus* (2003) **12,** 52–57.

Key words: thrombocytopenia; hemolitic anemia; danazol; lupus; treatment

Introduction

Patients with systemic lupus erythematosus (SLE) may develop several hematologic complications, including hemolytic anemia and thrombocytopenia. Both complications may be the initial manifestation of the disease and they may predate the appearance of other disease manifestations by several years.[1–3] Moreover, thrombocytopenia also increases the risk of SLE-related mortality.[4]

The conventional treatment for these manifestations associated with SLE are corticosteroids and splenectomy.[5,6] However, both entities can be refractory to both therapies. Danazol and cytotoxic drugs have been used in refractory cases.[7–12] Intravenous immunoglobulin as well as recombinant human interleukin-11 have also been used with success in

*Correspondence: JA Aviña-Zubieta, Unidad de Investigación en Epidemiología Clínica, Piso 10, Hospital de Especialidades CMN La Raza-IMSS, Seris y Zaachila SN, Col. La Raza, México, D.F. 02990, México.
E-mail: aavina100@hotmail.com
Received 1 July 2002; accepted 2 September 2002

10.1191/0961203303lu337oa

refractory cases; however; the transient effects and their high costs limit their use for chronic therapy.[13,14]

Several studies have evaluated the efficacy of danazol, corticosteroids, cytotoxic drugs in the management of thrombocytopenia as well as hemolytic anemia in SLE.[7–12,15] Most of these studies are case series and evaluated short term efficacy of a single drug.

The purpose of this study was to evaluate the long-term effectiveness of several drugs in the management of thrombocytopenia and hemolytic anemia secondary to SLE in a single center.

Patients and methods

Patients

The records of all patients who attended the outpatient clinic at the Rheumatic Disease Unit from January 1998 to December 1998 in our hospital and who met the following criteria were reviewed: (a) diagnosis of SLE according to the former American Rheumatism Association;[16] (b) diagnosis (currently or previously) of thrombocytopenia defined as platelet count less than 100 000 per mm^3, other causes of thrombocytopenia were excluded; (c) hemolityc anemia (currently or previously) defined as a fall in hemoglobin levels of at least 3 g/dl coincident with a rise in uncojugated bilirubin of at least 0.5 mg/dl, positive direct Coombs' test, and a reticulocyte count rate above 3%; (d) patients who had received treatment for thrombocytopenia and/or hemolytic anemia as initial therapy with the following drugs: prednisone (1–2 mg/kg/day for at least 4 weeks); azathioprine and oral cyclophosphamide (for a minimum of 8 weeks at a daily dosage of 1–2 mg/kg); intravenous cyclophosphamide (0.75 a 1 g/m^2/monthly for a minimum of 2 months); danazol (increasing doses from 200 to 1200 mg/day for at least 12 weeks); and dapsone 100–200 mg/day. All medical records were reviewed by one of us (JAAZ) between August 1998 and March 1999. Information on medication was recorded on a structured form. The starting date, stopping date, reason for discontinuation and side effects were recorded. Temporary discontinuations for any reason for a period less than one month were ignored. No information on the concomitant use of prednisone was recorded unless this was the established therapy for the hematological manifestations of SLE according to the treating rheumatologist.

The main outcome measures were time and cause of drug discontinuation according to the treating physician. In addition, time to first relapse (first new episode of thrombocytopenia and/or hemolytic anemia) after initial response was a secondary outcome measure.

Statistical analysis

Chi-squared tests with Yates' correction were used to compare differences between proportions. Two-tailed Fisher exact tests were used for 2×2 tables when appropriate. One-way analysis of variance was used to assess differences between means. Kaplan–Meier survival curves were used to estimate the probability of discontinuation for each drug. Each therapy course was considered to be independent from others. Patients who did not reach an end point and continued therapy at final follow-up were considered as censored as well as those who discontinued for other reason. Log-rank tests were used to test the hypothesis of equal survival among the drugs. All analysis were performing using SPSS for windows version 10.0.

Results

After all medical records were reviewed, 46 eligible cases were identified. From these, 41 (89%) had the

Table 1 Patient characteristics

Variable	*PDN* (n = *37*)	*DNZ* (n = *51*)	*CT* (n = *29*)	*Dapsone* (n = *4*)	P-*value*
Sex, female *n* (%)	46 (92)	34 (90)	27 (93)	4 (100)	N.S.
Age mean (years)	32.3	35.2	81.5	l33.3	N.S.
Disease duration[a]	26.5	57.1	81.5	101.3	0.008
Platelet count (mean)	35255	32400	30863	38333	N.S.
Rank selection, *n* (%)					
First	29 (78)	10 (19)	2 (7)	0	<0.001
Second	3 (8)	25 (49)	7 (24)	0	
Third	3 (8)	9 (18)	11 (38)	2 (50)	
Fourth	0	5 (10)	5 (17)	1 (25)	
Fifth	0	0	4 (14)	1 (25)	
Sixth	2 (5)	0	0	0	
Seventh	0	2 (4)	0	0	

PDN, prednisone; DNZ, danazol; CIT, cytoxic drugs (azathioprine, oral and intravenous cyclophosphamide, 6-mercaptopurine).
[a]Hematologic manifestations at the onset of therapy in months.

Table 2 Reasons for discontinuation. Percentages in parentheses are calculated over total number of treatments (*n*)

DROGA	n	*Total*	*Toxicity*	*Inefficacy*	*Both*[a]	*Other*
Prednisone	37	30 (83)	1 (3)	21 (57)	0	8 (22)
Danazol	51	31 (61)	6 (12)	10 (20)	1 (2)	14 (27)
Cytotoxic drugs	29	23 (79)	1 (3)	11 (38)	1 (3)	10 (35)
Dapsone	4	2 (50)	1 (25)	0	0	1 (25)

[a]Included as well in toxicity and inefficacy.

minimum required information. Thirty-four cases had thrombocytopenia (83%), two had hemolytic anemia (5%), and five had both disorders (12%). Current or past major involvement in the sample was as follows. Three patients had lupus neprhitis (class IV). From these, one also had had pleural effusion, and pneumonitis secondary to SLE. Twenty-three patients had mucocutaneous manifestations in addition to the hematological manifestations of SLE. From these, two patients also had pleural effusion and another had pulmonary embolism. In 14 cases the hematological disorder was the only manifestation of SLE. Finally, one case had had abdominal vasculitis.

Prednisone was the initial treatment in 34 patients (83%); pulses of methylprednisolone were prescribed in three cases (7%) followed by oral prednisone. If patients continued with this therapy for more than 4 weeks as a single therapy then it was considered for the long-term effectiveness study. If a new drug was started, then this drug was the one considered as the first used drug. Table 1 shows the patient and clinical characteristics of the study group. Overall, there were 121 drug prescribed cycles. Prednisone and danazol were the most frequent prescribed drugs (73%) followed by cytotoxic drugs (24%) and dapsone (3%). Prednisone was the first choice for treatment in 78% of the patients, while cytotoxic drugs and dapsone were never used as first or second choice.

Discontinuation of treatment

Causes of treatment discontinuations are shown in Table 2. Overall, at the time of data collection 86 (71%) of the 121 therapies were discontinued. The most frequent cause for discontinuation was inefficacy in all drugs but dapsone (35% of all drug prescriptions and 49% of all discontinuations).

Survival time analysis was conducted using the Kaplan–Meier product limit method to estimate the proportion of patients still receiving the various drugs at different points in time (Figures 1–3). There were statistically significant differences among the various drugs for all causes discontinuations (Figure 1). Overall, 25% of patients on danazol were still receiving the drug at 160 months, while 50% of patients on dapsone still received the drug at 45 months. Patients on prednisone and cytotoxic drugs had discontinued their treatments at 70 and 60 months, respectively. Mean times for discontinuations are shown in Table 3. Moreover, 50% of patients on prednisone and cytotoxic drugs had discontinued their therapies at 12 months for any reason. Figure 2 shows the

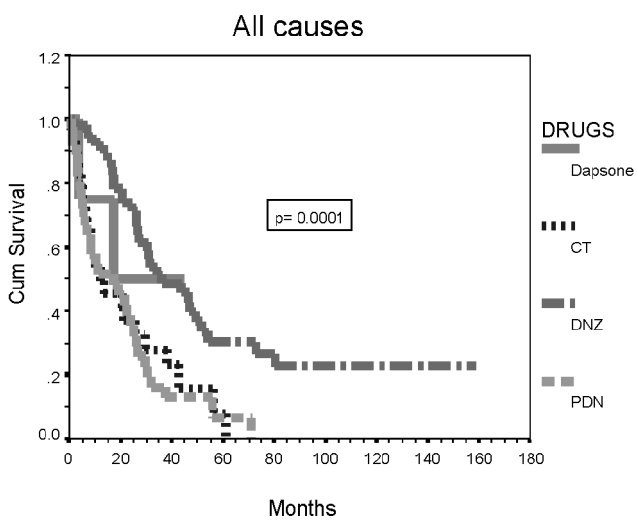

Figure 1 Survival curves for discontinuations due to any reason.

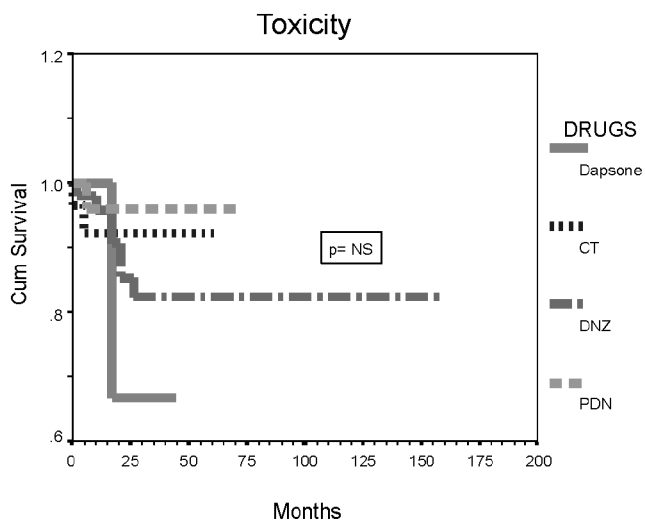

Figure 2 Survival curves for discontinuations due to toxicity.

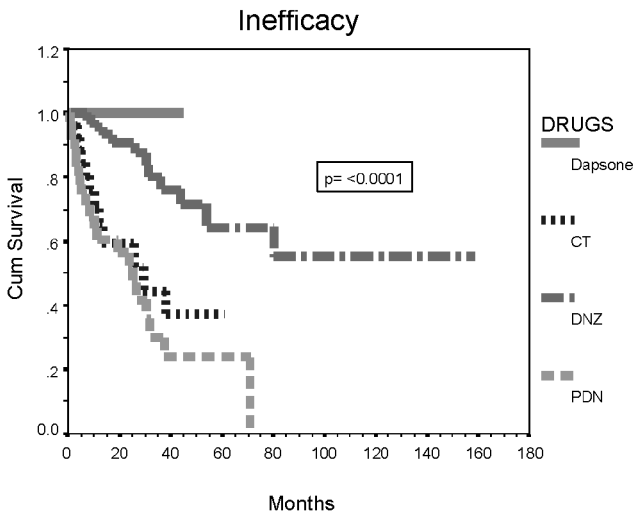

Figure 3 Survival curves for discontinuations due to inefficacy.

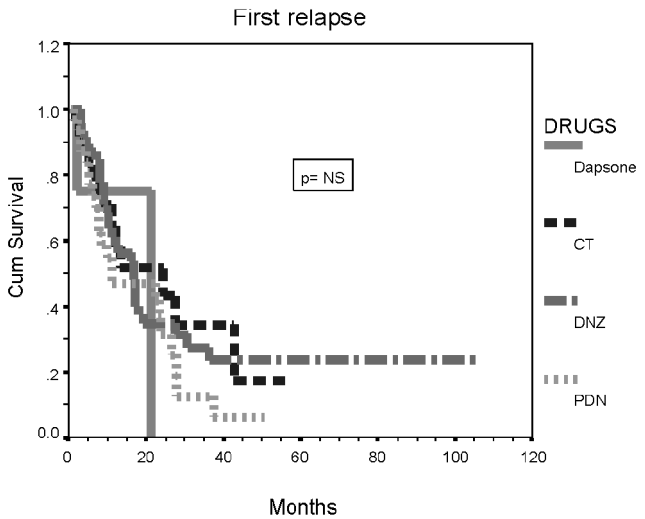

Figure 4 Survival curves for time to first relapse.

discontinuation for toxicity. There were no statistically significant differences among the several drugs. However, when survival curves were estimated for discontinuations due to inefficacy, there were statistically significant differences among the drugs with danazol having the lowest probability of discontinuation (Figure 3).

Relapses

There were 89 relapses among those who had an initial response. The time to first relapse (first new episode of thrombocytopenia and/or hemolytic anemia) after initial response is shown in Figure 4. There were not statistically significant differences among the various drugs using the long-rank test.

Adverse reactions

Overall, there were nine discontinuations due to toxicity (7.4%) in seven patients. Six cycles of danazol were discontinued due to side effects; four had hepatitis and two had rash and menstrual disturbances. One patient discontinued prednisone due to lack of efficacy and Cushing. One patient on azathioprine discontinued due to gastric intolerance and lack of efficacy. Finally one patient on dapsone discontinued the drug due to gastrointestinal intolerance.

Discussion

Corticosteroids and splenectomy are the standard treatment in autoimmune thrombocytopenia as well as in autoimmune hemolytic anemia. However, the efficacy of splenectomy in SLE is still under debate.[17–20]

All reported studies evaluating the efficacy of prednisone, danazol and cytotoxic drugs in the treatment of autoimmune hemocytopenia associated with SLE are case series and they report mainly short-term effects.[7–14] Moreover, comparisons among several drugs in the same set of patients have not been reported. Therefore, to our knowledge, this report is the first and the largest study comparing the long-term effectiveness of prednisone, danazol and cytotoxic drugs in autoimmune hemocytopenia secondary to SLE in the same setting of patients. Our study was based on prevalent cases seen in 1998, therefore a selection bias is likely to occur limiting generality of the results.

Because of the difficulties in conducting long-term clinical trials in patients with SLE, observational studies can provide information on the effectiveness of drugs used to treat SLE in the long-term. We defined as response for thrombocytopenia an increase in platelet counts above 100 000 and a rise in

Table 3 Mean times (months) for discontinuations among the several drugs

Drug	*All causes, mean (95% IC)*	*Toxicity, mean (95% IC)*	*Inefficacy, mean (95% IC)*
Prednisone	21 (13–27)	68 (63–73)	29 (19–40)
Danazol	62 (44–80)	134 (116–151)	107 (81–132)
Citotoxics	22 (14–30)	56 (52–62)	33 (22–43)
Dapsone	28 (10–45)	35 (21–50)	All censored

hemoglobin levels at least to the values prior to the hemolysis for those cases with hemolytic anemia. These criteria are more strict than those used for other groups.[5–12]

In 34 cases (83%) hematological manifestations occurred within 6 months after the onset of SLE. Moreover, these manifestations were the initial sign of SLE in seven patients (17%). This suggest that hemocytopenia occurs early in SLE. Oral prednisone was prescribed in the 34 out of 41 patients (83%) during the acute phase of the disease. Seven patients received boluses of methylprednisolone (1 g/day/3 days) as the acute treatment (data not shown). Only those treatments which were continued for more than 4 weeks were then considered as drugs selected in rank one.

Survival analysis showed that 50% of the cycles were discontinued around 20 months. Danazol had the higher probability of continuation mainly owing to fewer discontinuations due to inefficacy. Thus, danazol seems to be the drug with best effectiveness in the long term. Since rank selection (sequential order in which the drugs were received) might bias the results, we built survival curves for each cause of discontinuation among the drugs using rank selection (first *vs* other) to estimate proportions of patients still receiving the drugs at different points in time. We did not find statistically significant differences among the drugs evaluated in this study (data not shown). It has been suggested that early treatment may be more effective in the long-term management of autoimmune thrombocytopenia.[6] However, when we plotted duration of hematological manifestations prior to the onset of therapy (less than 1 year *vs* more than 1 year), we did find statistically significant differences for discontinuations due to all causes as well as inefficacy only for danazol. Nevertheless, in the multivariate analysis (Cox regression) using disease duration, rank and drugs as covariates; the only significant variable was drug (data not shown).

Owing to the fact that there were only four cases with dapsone, we performed all the previous analyses excluding these cases (sensitivity analysis) and the results did not change at all.

Concomitant use of steroids may improve continuation rates. We did not record use of prednisone unless this was the established therapy for the hematologic manifestations of SLE, therefore we were unable to test this hypothesis with our data.

It can be argued that severity of thrombocytopenia might influence drug selection as well as treatment response. Half of the patients (49.5%) had platelet counts less than 20 000 and they were equality distributed among the several drugs evaluated in this study. Furthermore, when we plotted platelet counts ($<20\,000$ *vs* $>20\,000$) for each cause of discontinuation, there were not statistically significant differences among the drugs evaluated in this study.

To the best of our knowledge, the use of dapsone in the management of hemocytopenia secondary to SLE has not been previously reported. However its use in the treatment of immune thrombocytopenia other than SLE has shown to be effective.[21,22]

Intravenous immunoglobulin is a reasonable alternative in patients who fail to respond to other treatments. The response, however, often lasts only a few days, and maintenance therapy may be required to maintain platelet count above 30 000 µl. Moreover, its high cost limits its use. In our unit, we do not use intravenous immunoglobulins for the treatment of hematological manifestations of SLE, therefore, we were unable to evaluate the long-term effectiveness of this therapy.

In summary, in this study crude rates of discontinuation were different for each drug the main cause of discontinuation was inefficacy for all drugs. Using the Kaplan–Meier curves to estimate probability of continuation at different points in time, danazol had the best survival. Therefore if we use rates of discontinuation as a measure of effectiveness, the long-term effectiveness among danazol, corticosteroids, cytotoxic drugs, and dapsone are different, with danazol having the best profile. Dapsone seems to be effective in the management of hematological manifestations of SLE and requires further investigation.

Acknowledgement

The authors would like to thank Lic Verónica Soto for her help in the retrieval of the references reviewed in this manuscript.

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