Initial Treatment of Immune Thrombocytopenic Purpura with High-Dose Dexamethasone

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ABSTRACT

BACKGROUND

The role of high-dose dexamethasone in the treatment of immune thrombocytopenic purpura in adults is controversial. We assessed the effectiveness of high-dose dexamethasone as initial treatment in a series of consecutive adults with immune thrombocytopenic purpura.

METHODS

Consecutive patients with newly diagnosed immune thrombocytopenic purpura and a platelet count of less than 20,000 per cubic millimeter or a platelet count of less than 50,000 per cubic millimeter and clinically significant bleeding were enrolled between January 1997 and December 2000. Oral dexamethasone at a dose of 40 mg per day for four consecutive days was the initial treatment. A response was defined as an increase in the platelet count of at least 30,000 per cubic millimeter and a platelet count of more than 50,000 per cubic millimeter by day 10 after the initiation of treatment. A sustained response was defined as a platelet count of more than 50,000 per cubic millimeter six months after the initial treatment.

RESULTS

Of 157 consecutive patients, 125 were eligible. The mean (±SD) platelet count before treatment was 12,200±11,300 per cubic millimeter. A good initial response to high-dose dexamethasone occurred in 106 of the 125 patients (85 percent): the platelet count increased by at least 20,000 per cubic millimeter by the third day of treatment, and the mean platelet count was 101,400±53,200 per cubic millimeter (range, 50,000 to 260,000 per cubic millimeter) one week after the initiation of treatment. Among the 106 patients with a response, 53 (50 percent) had a sustained response; the other 53 (50 percent) had a relapse within six months, most of them (94 percent) within the first three months. A platelet count of less than 90,000 per cubic millimeter on day 10 was associated with a high risk of relapse. The treatment was well tolerated.

CONCLUSIONS

A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura.

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IMMUNE THROMBOCYTOPENIC PURPURA results from antiplatelet autoantibodies, usually of the IgG class, that cause platelet destruction in the reticuloendothelial system.[1] Corticosteroids, in a dose equivalent to 1 to 2 mg of prednisone per kilogram of body weight daily, increase the platelet count in about 75 percent of adults and are the conventional initial treatment for immune thrombocytopenic purpura.[2,3] Since most responses occur after 7 to 10 days of treatment, the lack of a clinically significant increase in the number of platelets after three weeks of treatment is considered to represent failure of corticosteroid treatment.[1,4] Many patients have a relapse when the dose of corticosteroids is reduced; less than 5 percent to more than 30 percent of patients have sustained remission, depending on the duration of the disorder, the criteria used to define a response, and the duration of follow-up.[1-5] Debilitating side effects are common when long-term corticosteroid therapy is required to maintain the platelet count, and serious infections have been observed in patients who have received daily prednisone treatment for only several weeks.[6,7] Nevertheless, no other therapy for immune thrombocytopenic purpura is associated with a higher rate of initial remission or is more cost effective than corticosteroids.

A short course of high-dose dexamethasone has been tried in patients with refractory immune thrombocytopenic purpura, but its efficacy is controversial.[8-10] In this study, we tested the effectiveness of high-dose dexamethasone (40 mg per day for four consecutive days) as initial treatment in adults with immune thrombocytopenic purpura.

METHODS

STUDY PATIENTS

Consecutive patients at the Prince of Wales Hospital in Hong Kong who were given a diagnosis of immune thrombocytopenic purpura between January 1997 and December 2000 and required treatment were enrolled in this study. Immune thrombocytopenic purpura was diagnosed according to the practice guidelines of the American Society of Hematology.[3] All patients had either a platelet count of less than 20,000 per cubic millimeter or clinically significant mucosal bleeding and a platelet count of less than 50,000 per cubic millimeter. The criteria for exclusion were relapsed immune thrombocytopenic purpura; treatment with corticosteroids during the previous six months; a history of clini-

cally significant adverse effects of previous corticosteroid treatment, such as psychosis or avascular necrosis of bone; uncontrolled hypertension or diabetes mellitus; active infection; and pregnancy. Oral informed consent was obtained from all patients. We chose to conduct a cohort study rather than a randomized study, because patients were aware of and apprehensive about the side effects of long-term high-dose prednisone therapy. The study was approved by the institutional review board of the Department of Medicine and Therapeutics, Chinese University of Hong Kong.

TREATMENT PROTOCOL

Patients received 40 mg of oral dexamethasone daily for four consecutive days. The three criteria for an initial response were an increase in the platelet count of at least 30,000 per cubic millimeter, a platelet count of more than 50,000 per cubic millimeter by day 10 after the initiation of treatment, and cessation of bleeding. Unresponsiveness was defined as an increase in the platelet count of less than 30,000 per cubic millimeter or a platelet count of 50,000 per cubic millimeter or less by day 10. Other treatments were considered if there was no response to dexamethasone. If the patient had a platelet count of more than 50,000 per cubic millimeter after four days of dexamethasone treatment, no further treatment was given. The patients had outpatient follow-up visits monthly for two months and then every two to three months. A sustained response was defined as a platelet count that remained above 50,000 per cubic millimeter after six months of follow-up. If the platelet count dropped below 30,000 per cubic millimeter within the first six months, another four-day course of dexamethasone was given, followed by 15 mg of prednisone daily, with gradual tapering. Patients whose platelet counts could not be maintained at 30,000 per cubic millimeter or higher with less than 10 to 15 mg of prednisone daily were offered other treatments.

LABORATORY STUDIES

Complete blood counts were obtained at recruitment; during high-dose dexamethasone treatment; on day 7, 8, 9, or 10; and during follow-up visits. Fasting and postprandial blood glucose levels were measured at recruitment and after treatment with high-dose dexamethasone. Urinalysis, renal-function and liver-function tests, and serologic tests for hepatitis B and hepatitis C were performed at the time of recruitment. Bone marrow aspiration was

not performed routinely but was performed before other treatment was initiated in all patients who did not have a response to high-dose dexamethasone.

STATISTICAL ANALYSIS

The group of patients with a sustained response at six months and the group of patients who had a relapse within six months were compared with respect to age, sex, and the platelet counts before treatment; on days 3, 4, and 10; and three months after treatment. These comparisons were made to determine whether these variables were predictive of a sustained clinical response. Numerical data were compared with the use of Student's t-test for independent samples, and categorical data were compared with the use of the chi-square test. Differences were considered to be significant at the level of $P<0.05$. All reported P values are two-sided. All other values are means ±SD unless otherwise indicated.

RESULTS

STUDY PATIENTS

Between January 1997 and December 2000, 157 patients were given a diagnosis of immune thrombocytopenic purpura at the Prince of Wales Hospital. In 21 of these patients, the episode was a relapse of immune thrombocytopenic purpura, and these patients were excluded. Eleven other patients were also excluded — five because they had systemic lupus erythematosus, two because of active mycobacterial infection, two because they had recently received corticosteroid therapy for asthma, and two because of major gastrointestinal bleeding due to peptic ulcer. The remaining 125 patients with newly diagnosed immune thrombocytopenic purpura were enrolled in the study.

The median age of these 125 patients was 44 years (range, 17 to 84); 85 were female, and 40 were male. Five patients had essential hypertension, two patients had type 2 diabetes mellitus, and another two patients had both type 2 diabetes mellitus and essential hypertension.

RESPONSE TO THERAPY

The mean platelet count before treatment was 12,200±11,300 per cubic millimeter (range, 1000 to 48,000 per cubic millimeter). Of the 125 eligible patients, 106 (85 percent) had an initial response to high-dose dexamethasone: the platelet count had increased by at least 20,000 per cubic millimeter by th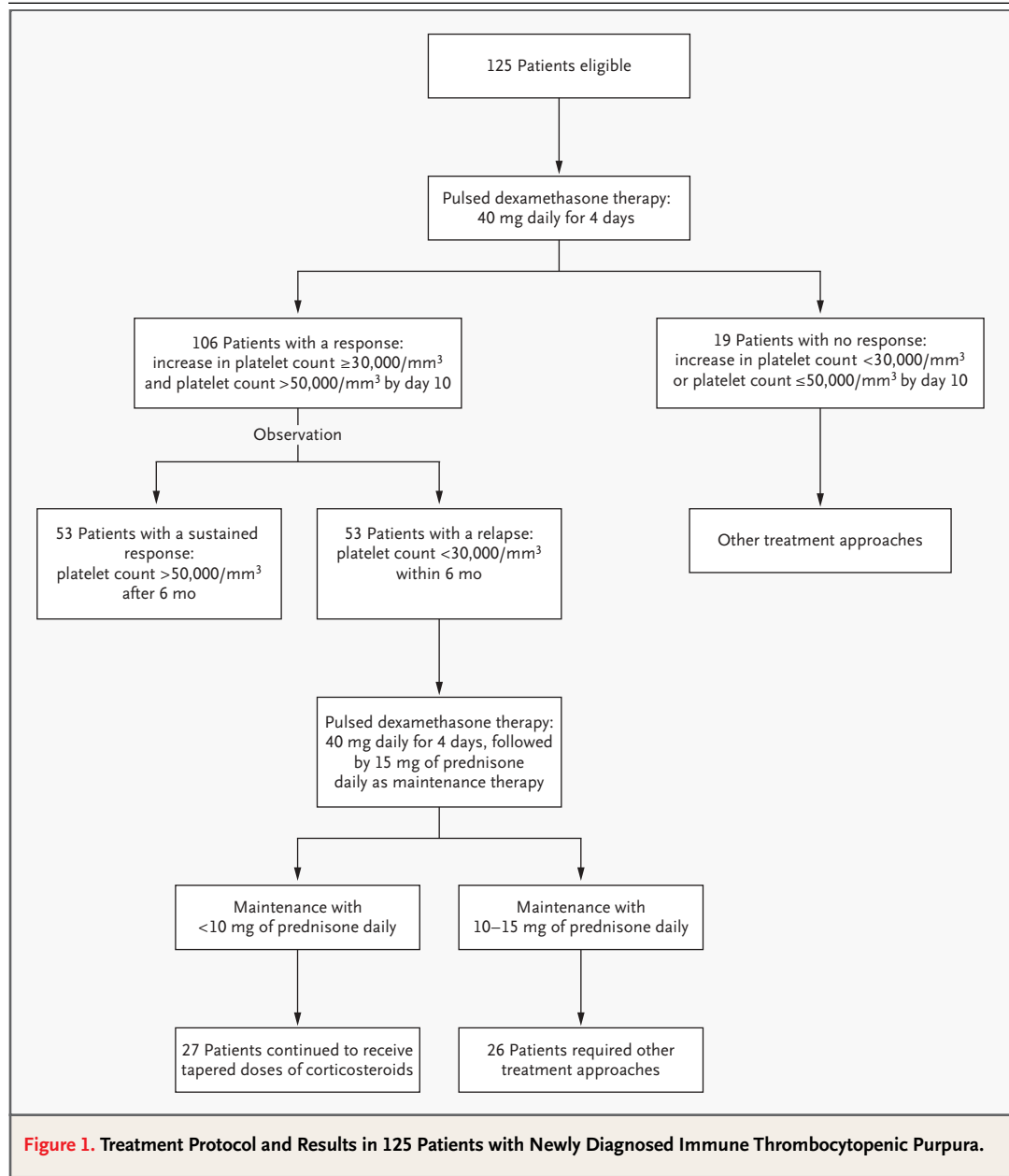e third day of treatment, and the mean platelet count was 101,400±53,200 per cubic millimeter (range, 50,000 to 260,000 per cubic millimeter) one week after the initiation of treatment in this group of 106 patients (Fig. 1). The 19 patients who did not have a response to dexamethasone (i.e., the platelet count increased by less than 30,000 per cubic millimeter or was no more than 50,000 per cubic millimeter by day 10) received further treatment with intravenous immune globulin (in 7 patients) or anti-D immune globulin (in 12 patients). Five of these 19 patients did not have a response to immune globulin treatment and subsequently underwent splenectomy or received combination cytotoxic therapy.

FOLLOW-UP

The median follow-up period was 30.5 months (range, 13.0 to 59.5 months). No patients were lost to follow-up. Among the 106 patients with a response to dexamethasone therapy, 53 (50 percent) had a sustained platelet count of more than 50,000 per cubic millimeter after a single course of high-dose dexamethasone therapy and required no further treatment during two to five years of follow-up (Fig. 1). The remaining 53 patients had a relapse (a platelet count of less than 30,000 per cubic millimeter) within six months. The median time to relapse was 45 days (range, 14 to 129 days). Fifty of these patients had a relapse within the first three months after the four-day treatment with dexamethasone.

All patients with a relapse had a response to a second course of high-dose dexamethasone therapy, with the platelet count increasing to more than 50,000 per cubic millimeter within one week after the second treatment. The platelet count in 27 of these 53 patients who had had a relapse remained higher than 50,000 per cubic millimeter during maintenance therapy with 10 mg or less of prednisone daily (median, 7.5 mg); in 5 of these 27 patients, the platelet count remained higher than 50,000 per cubic millimeter for more than six months after the discontinuation of maintenance therapy. The other 26 patients required more than 10 mg of prednisone daily for the maintenance of a platelet count higher than 50,000 per cubic millimeter and required other forms of treatment; 11 patients eventually underwent splenectomy.

The mean platelet count 10 days after the start of the initial course of dexamethasone therapy was 132,600±41,900 per cubic millimeter among the patients who had a sustained response and 84,700±

Figure 1. Treatment Protocol and Results in 125 Patients with Newly Diagnosed Immune Thrombocytopenic Purpura.

37,000 per cubic millimeter among the patients who had a relapse. The difference between these two groups was statistically significant (P<0.001). The two groups were similar with respect to age, sex, the pretreatment platelet count, the platelet count at day 3 (Table 1), and the increase in the platelet count at day 3. A platelet count of less than 90,000 per cubic millimeter at day 10 was associated with a relapse rate of 70 percent, whereas less than 20 percent of patients with a platelet count of

more than 120,000 per cubic millimeter at day 10 had a relapse.

Overall, 45 of the 125 patients (36 percent) required additional treatment with splenectomy, intravenous immune globulin, anti-D immune globulin, danazol, vinca alkaloids, alkylating agents, or cyclosporine. This group included the 19 patients who did not have an initial response to high-dose dexamethasone and the 26 patients who had a relapse and required maintenance therapy with high-

dose prednisone. Of the 26 patients who had a relapse within the first two months and had a platelet count of less than 90,000 per cubic millimeter at day 10, 21 required additional therapy, as compared with 5 of the other 80 patients who had an initial response (P=0.001).

SIDE EFFECTS

High-dose dexamethasone therapy was well tolerated. No patient reported side effects that were severe enough to necessitate the discontinuation of treatment. Nine patients with essential hypertension, type 2 diabetes mellitus, or both tolerated the medication well. Only one patient with diabetes mellitus needed an increase in the dose of the oral hypoglycemic agent.

DISCUSSION

There have been numerous retrospective studies of corticosteroid treatment in adults with immune thrombocytopenic purpura,[11,12] and despite the variations in the criteria for inclusion, treatment, and response in these studies, it is possible to draw several general conclusions. Spontaneous remissions are rare, and the response rate ranges from 65 to 85 percent. Most responses occur within 7 to 10 days, with a peak in the platelet count within 2 to 4 weeks. The lack of a substantial increase in the platelet count by three weeks is generally considered to indicate treatment failure, although responses have been observed after six months in a few patients.[13] Sustained responses after the discontinuation of conventional corticosteroid therapy occur in 5 to 30 percent of patients.[1-5] The usual treatment for adults with immune thrombocytopenic purpura is prednisone, at a dose of 1 to 2 mg per kilogram daily, or its equivalent. Mazzucconi et al.[14] compared a low-dose regimen (0.5 mg of prednisone per kilogram per day) with a high-dose regimen (1.5 mg per kilogram per day) and noted no significant difference in the rate of sustained responses (30 percent vs. 34 percent). Bellucci et al.[15] reported similar response rates among patients who received 0.25 mg per kilogram per day and those who received 1 mg per kilogram per day.

Andersen[8] used a short course of high-dose dexamethasone to treat 10 adults with refractory immune thrombocytopenic purpura and found it highly effective and well tolerated. With six cycles of high-dose dexamethasone, Khouri et al.[9] reported complete remission that lasted for as long as

Table 1. Univariate Analysis of Clinical and Laboratory Variables Associated with the Outcome at Six Months among the 106 Patients with an Initial Response.*

Variable	Sustained Response at 6 Mo	Relapse within 6 Mo	P Value
Age (yr)	46.7±18.2	45.8±18.5	0.80
Sex (no.)			0.31
Female	33	40	
Male	20	13	
Platelet count (per mm³)			
Pretreatment	12,300±11,600	13,500±11,800	0.63
Day 3	46,700±16,500	42,100±23,400	0.34
Day 10	132,600±41,900	84,700±37,000	<0.001
3 Mo	185,100±73,400	59,100±57,500	<0.001

* Plus–minus values are means ±SD.

four years in two of three adults who had had relapses of chronic immune thrombocytopenic purpura. Wali et al.[16] have also reported that high-dose dexamethasone was effective in patients with chronic immune thrombocytopenic purpura. However, others have failed to confirm these favorable results.[10,17-20] All these studies were conducted in patients with resistant or refractory cases and involved a small number of patients.

We evaluated the effectiveness and side effects of a four-day course of dexamethasone as initial treatment in 125 adults with immune thrombocytopenic purpura. Eighty-five percent of these patients had a good initial response to dexamethasone, with platelet counts increasing to a safe level in 106 patients by the third or fourth day after treatment began. This response rate is similar to the rate reported with conventional corticosteroid therapy.[12] About 42 percent of our patients had a sustained response after just one four-day course of high-dose dexamethasone therapy and hence had fewer side effects than are usual in patients who receive conventional doses of prednisone for longer periods. Moreover, with our protocol, we were able to identify corticosteroid treatment failure much earlier than is possible with conventional prednisone treatment. We found that a delayed response was unlikely to occur more than one week after the failure of a four-day course of high-dose dexamethasone therapy. It might be argued that our protocol

may prematurely declare corticosteroid treatment to have failed; however, the initial failure rate (15 percent) and the proportion of patients who required splenectomy or additional therapy (36 percent) in our study were no higher than the rates with conventional corticosteroid treatment.

A sustained response may be achieved in about 30 to 40 percent of adults with immune thrombocytopenic purpura with the use of various corticosteroid regimens. The use of our high-dose dexamethasone regimen may identify this group of patients who are likely to have a response and expose them to only a short course of corticosteroid therapy. More than 70 percent of our patients with a platelet count of less than 90,000 per cubic millimeter at day 10

had a relapse within six months. The occurrence of a relapse within two months and a low platelet count at day 10 were associated with corticosteroid treatment failure and the need for other treatment. A prolonged remission might have been attainable with further courses of high-dose dexamethasone therapy in some of our patients who had no response to the initial course of dexamethasone therapy or who had a relapse, as Andersen has suggested.[8]

In summary, a four-day course of high-dose oral dexamethasone is an effective initial treatment for immune thrombocytopenic purpura in adults. Long-term remission is obtained in more than 40 percent of patients after a single course of this treatment.

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