

LONG TERM FOLLOW-UP OF 26 PATIENTS WITH ADULT IDIOPATHIC THROMBOCYTOPENIC PURPURA

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SUMMARY

Purpose: To assess the long-term results of therapy in patients with adult idiopathic thrombocytopenic purpura (ITP). **Methods:** Twenty six adults with ITP were evaluated for their response to corticosteroid therapy, splenectomy and danazol therapy. **Results:** Our overall long term response to corticosteroids and splenectomy was 76 %. In refractory patients, danazol therapy provided an overall response rate of 57 %. **Conclusion:** Corticosteroid therapy and splenectomy have been the primary and most effective treatments of ITP in adults. In patients who do not respond or relapse after corticosteroid therapy or splenectomy, treatment remains a challenge. Our experience suggests that danazol is less toxic and an effective alternative for long term medical therapy of chronic refractory ITP, especially in splenectomized patients.

Key Words : Idiopathic Trombocytopenic Purpura, Adrenal Cortex Hormones.

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an immunologically mediated destructive thrombocytopenia, in which antibody sensitized platelets are destroyed prematurely in the reticuloendothelial system. The clinical diagnosis is made after excluding the presence of other disorders known to be associated with shortened platelet survival. The majority of patients with ITP respond to treatment with corticosteroids or to splenectomy. In patients who do not respond or relapse after corticosteroid therapy or splenectomy, treatment remains a challenge and

the frequency of death from hemorrhage in these patients is about 5 % (1,2,3,4). This article describes our experience in the treatment of adult ITP.

MATERIALS AND METHODS

Patient Selection. The findings in 20 female and six male patients with ITP seen at the Hematology Department of Gazi University Medical School are reported. The criteria for the diagnosis of adult ITP were (i) 16 years of age or older (ii) thrombocytopenia lasting two weeks or more in conjunction with a normal white cell count and no anemia except when there was

active bleeding (iii) normal or increased numbers of megakaryocytes in the bone marrow, and (iv) a nonpalpable spleen, no recent ingestion of drugs that could be implicated and no alternative explanation for the thrombocytopenia. (1,3).

Patients who responded to therapy were excluded from the study if the follow-up period was shorter than two years after discontinuation of corticosteroids; six months after splenectomy and other treatments. Patients who died due to disease and / or therapy were also included.

Definition of Therapeutic Response

1) Complete response (CR): An increase in platelet count to $150 \times 10^9/L$ or more.

2) Permanent complete response (pCR): CR continuing for more than two years after discontinuation of corticosteroid therapy and for more than six months after splenectomy.

3) Temporary complete response (tCR): A complete response with an eventual relapse as manifested by a platelet count persistently below $150 \times 10^9/L$.

4) Continuing complete response (c CR): A complete response with the platelet count continuing above $150 \times 10^9/L$ at the most recent evaluation.

5) Partial response (PR): An increase in platelet count to at least $50 \times 10^9/L$ but less than $150 \times 10^9/L$. PR is further divided as permanent PR (pPR), temporary PR (tPR) and continuing PR (cPR) like CR.

6) No response (NR): A failure of the platelet count to increase to a minimum of $50 \times 10^9/L$.

Criteria for Refractory ITP:

Patients who failed steroids and splenectomy and did not maintain safe platelet counts ($>30,000$) were regarded as refractory ITP (5).

Therapeutic Program :

Criteria for starting therapy were : The presence of hemorrhagic complications and /or thrombocytopenia lower than $30 \times 10^9/L$.

Corticosteroids. Prednisolone or another equivalent corticosteroid was given to all patients at a daily dosage of 1-2 mg/kg/day as initial therapy for two to four weeks. In patients in whom a response was achieved, corticosteroid dosage was gradually tapered over two months.

Splenectomy. Surgery was performed in patients who failed to develop a permanent response with corticosteroids (except for those

who refused surgery). Before surgery all patients were vaccinated with pneumococcal and H. influenza vaccines. Patients who failed to respond or who relapsed after response were evaluated for the presence of an accessory spleen by scanning.

Therapy for Refractory ITP:

Danazol . Danazol (Danasin, Koçak, Turkey) was given orally at a dosage of 200 mg tid for at least three months in patients refractory to steroids and splenectomy or who refused surgery. Patients who failed to respond to danazol were evaluated for the efficacy of low dose corticosteroids.

RESULTS

At diagnosis the mean age was 35 (range 16 to 75 years) and the female/male ratio was 3.3:1. The mean platelet count was $14 \times 10^9/L$ (range 1 to $57 \times 10^9/L$). Abnormal bleeding or bruising was the presenting complaint in all patients. Five patients had major bleeding at diagnosis (vaginal bleeding). One patient aged 75 died of upper gastrointestinal bleeding on day seven of corticosteroid therapy with partial response. One patient with a platelet count of $57 \times 10^9/L$ was followed for 20 months without therapy.

Initial CR, PR and failure rates to corticosteroid therapy in 25 patients were 32 %, 44 % and 24 % respectively. Overall long term response to corticosteroid therapy was 16 %. (Table 1)

Seventeen patients who failed to respond to corticosteroid therapy and accepted splenectomy were evaluated for response. Initial CR, PR and failure rates to splenectomy were 82 %, 6 %, 12%, respectively. Overall prolonged response rate (CR+PR) was 70%. Splenectomy was well tolerated. There were no surgery related mortality. Five of the 17 patients in whom splenectomy failed to induce a remission were evaluated for the presence of an accessory spleen by scanning. An accessory spleen was demonstrated in one of five patients and this patient failed to respond after accessory splenectomy. Overall long term response to corticosteroids and splenectomy was 76 %. Five patients (24 %) had refractory ITP. Seven patients, five refractory ITP and two who refused

Table 1: Total response to the different treatments used in adults with ITP.

Treatment	No of cases	pCR	pPR	Failure	cCR	cPR
Cs	25	2 (8%)	2 (8%)	21 (84%)		
Splenectomy	17	9 (53%)	3 (17%)	5 (30%)		
Danazol 7				3 (43%)	2 (28.5%)*	2 (28.5%)*
Low dose cs	3			1 (33%)	2 (67%)	

Cs = corticosteroid

* with daily 600 mg danazol

surgery, were treated with danazol 600 mg daily. Initially five of seven patients achieved a CR (71 %). In the last evaluation cCR and cPR rate was 57% (Table-1). Danazol therapy was well tolerated and the only side effect noted was mild liver dysfunction. The mean duration of danazol therapy was 10 months (range 3 to 19 months). Two unsplenectomized patients did not respond to danazol initially and one patient failed after 12 months of CR.

DISCUSSION

Adult ITP treatment strategies are different from those for children as spontaneous remission is unusual. Available evidence suggest that only about 5% of adults with ITP have spontaneous remission. Therefore adult patients with moderate to severe thrombocytopenia are generally treated immediately after diagnosis (6).

First line treatment is usually with steroids at a dosage of 1 to 2 mg/kg prednisolone per day. The initial response rate to steroids is about 80 %. With shorter follow-up intervals higher remission percentages are noted (1,3,7,8). The actual long term response is more likely to be 10 % to 20 % (5). In our patients the initial response rate was 76% and permanent response rate at two years was 16%.

Response rates to steroid therapy achieved in this study were similar to those previously reported. Although a favorable response with symptoms less than 14 days of duration was reported (1), we were not able to demonstrate such an association.

Following a demonstrated lack of response to corticosteroids, splenectomy has usually been considered as second line treatment. Splenectomy results in a much higher cure rate than any medical regimen. Approximately two thirds of adults achieve a permanent response following splenectomy (3,5,6,9,10). Half of the relapses occur within six months of splenectomy

(6). Surgical mortality from splenectomy should approach zero if the surgeon is experienced (5).

Initial CR and PR rates in our patients were 82% and 6% respectively. Six months after splenectomy the CR rate fell to 53%. Overall long term response to splenectomy was 70 % and it was similar to those previously reported.

Refractory patients, who comprise about 25% to 30 % of patients with ITP, respond poorly to subsequent treatment, and have significant mortality and morbidity (1,5).

Danazol, a synthetic testosterone derivative, has also been used with some success in chronic ITP. Ahn et al. showed an overall response rate of 61%. Hepatic complications associated with danazol therapy rarely limited its usage (11). The benefits of danazol have not been confirmed by all groups in chronic ITP (2,12). Our overall response rate to danazol was 57% which was similar to Ahn et al. Mild liver dysfunction was the only side effect noted but did not limit its usage.

Two of three patients who did not respond to danazol were in cCR with low dose corticosteroid (< 10 mg prednisolone) treatment. One patient who failed low dose corticosteroid had been treated with intravenous immunoglobulin (IVIG) during bleeding episodes.

In summary, corticosteroids and splenectomy have been the primary and most effective treatments of ITP in adults. In patients who refused surgery or with refractory ITP, various other therapeutic measures have been advocated. The effects of IVIG and anti-D (2,8,10,13) are usually transient. Cytotoxic chemotherapy yields a low remission rate and has mutagenic potential (14,15). Our experience suggest that danazol is a less toxic and more effective alternative for long term medical therapy of chronic ITP especially in splenectomized patients.

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