



Original Article

Treatment of Chronic Refractory ITP with Danazol

M R Z Khan¹, M A Aziz², S U Shah³, M Begum⁴, I Mahmood⁵, A B M Yunus⁶

Abstract

50 patients of chronic ITP were registered in Hematology Department, BSMMU, Dhaka. During this study period (1 yr.) among 50 patients 30 (60 %) were female & 20 (40%) were male. 56 % patients were belong to 21- 40 yrs & 32 % were between 15- 20 yrs. In this study 50 patients were selected who are refractory to corticosteroid, azathioprine, and cyclophosphamide but none were splenectomized. Patients were above 15 yrs. and have long history of ITP (2 yrs) . Out of 50, 48 patients treated with danazol for 12 wks (200- 600mg/day). Patients were followed up on day 7 & 4 wkly up to 12 wks for platelet count, bleeding manifestation & toxicities. Treatment was started to 50 selected patient but 2 patients discontinued the therapy after first dose and remaining 48 patients were completed the therapy. After starting of danazol on day 7, response rate was 79.2 % (platelet count raised in 38 patients out of 48).On 4th week follow up, 25 % (12 patients) achieved (CR) complete remission (platelet count \geq 1,50,000/cmm), 62.5 % (30 patients) achieved (PR) partial remission(platelet count \geq 50,000- <1,50,000/cmm) and 6 had no response at all. On 8th week, 7 patients remained in CR (14.6 %), 5 in relapsed remained in partial remission. 14.5 % (7) patients remained in CR, 10.4 % (5) in relapsed remained in partial remission on 12th week. Overall result out of 50 patients (2 excluded who were not attended for follow up & 6 were not responded at all) CR 14.5% (7 patients), PR 72.9 % (35 patients).It is cleared from this study & supported by other studies that danazol promptly raised platelets count within 5-10 days with excellent response (79.2%).

TAJ 2009; 22(1): 93-96

Introduction

The incidence of chronic ITP is about 10 in every 100,000 and is most often in adults with female predominance^{1,2,3}. Corticosteroid is the mainstay of treatment but unfortunately thrombocytopenia usually recur when treatment is discontinued.

Splenectomy is the definitive treatment with permanent response in more than 70% of patients^{4,5}. Immunosuppressive drugs including vinca

alkaloid will often produce response where above treatment fail (Refractory) or when they are impractical or contraindicated. With IV Vincristine, improvement occurs in more than half of the patient refractory to prednisolone or splenectomy⁶. Most subsequent studies also found relatively high rates but the majority of response were transient^{3,7}. Danazol^{12,13} is a synthetic steroid derived from ethisterone. It is an attenuated

¹ Deputy Chief Medical Officer, Rajshahi University Medical Centre, Rajshahi.

² Assistant Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

³ Assistant Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

⁴ Associate Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

⁵ Associate Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.

⁶ Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka

androgen, has been effective in increasing platelet counts in patient with ITP. The mechanism of action is induced reduction of of Fc receptors on phagocytic cells.

Material and Methods

Study was carried out on 50 Patients of chronic idiopathic thrombocytopenic purpura attending in the Department of Hematology , Bangabandhu Sheik Mujib Medical University, Dhaka, Bangladesh, who came from different parts of Bangladesh during the period of January 2004 to August 2006 . Inclusion criteria were (1).Chronic isolated thrombocytopenia with normal or increased numbers of bone marrow megakaryocytes (2). Absence of splenomegaly & of any underlying disorder (3). Drug history & coagulopathy was absent (4) Patient's age were 15 yrs or more and refractory to prednisolone and other drugs.

(5). Patient who did not agree to do splenectomy or impractical or contraindicated. Baseline investigations before treatment were Hemoglobin, ESR, total count of WBCs & Platelet, antinuclear factor, Lupus erythematosus (LE) cell test, blood sugar estimation, liver function test and renal function test .All patient received Danazol (200 mg-600 mg/day) up to 24 weeks and were followed up at least 12 weeks.

Results

Most of the patients 60 % were female and 40 % were male, 56 % patient were between 21 to 40 yrs , 32 % were between 15 to 20 yrs, 4 % were more than 50 years. All patients presented with purpura and easy bruise , 80 % have gum bleeding & epistaxis, subconjunctival hemorrhage (30 %),

haematuria (20%), anemia (4%) & retinal haemorrhage (2%).

Full blood counts were normal except thrombocytopenia, prolong bleeding time. Antinuclear factor was absent and LE cell test was negative. Antiplatelet antibodies was not detected because there is lack of facility.Out of 50 patients 7 (14.5%) were in complete remission and 35 (72.9%) were in partial remission after danazol.Total responder after 1st dose was 79.2 % . On 4th week among 48 patients 12 were (25%) in CR, 62.5 % (30) in PR and 6 not responded. On 8th week follow up among 12 patients, 7 patients remained in CR

(14.6%), 5 in relapsed remained in partial remission .On 12th week follow up 7 patients remained in CR (14.5%), 5 (10.4%) in relapsed remained in partial remission .Overall result, out of 50 patient (2 were excluded who did not continue the therapy after 1st dose), 7 patients (14.5 %) remained in CR , 35 (72.9 %) in PR, and six (12.5 %) did not show any response.

Table-1. Clinical presentation of ITP patients attended in HOPD.

Clinical presentation	No.of patients	percentage
1.Petechiae, purpura, bruise	50	100
2.Epistaxis, gum bleeding	40	80
3.Subconjunctival haemorrhage	15	30
4.Menorrhagia	15	30
5.Haematuria	10	20
6.Anaemia & weakness	2**	4
7. Malena	1	2
8.Haemoptysis	1	2
9. Visual disturbance (retinal haemorrhage)	1	2
10.Neurological symptoms	0	0

Table-2. Hematological profile of ITP patients(N=50).

Test	Comment
Hemoglobin	Normal in 48 patients. Reduced in 02 patients.
ESR	Normal in all patients.
TC of WBCs	Normal 35
TC of platelets	< 30×10 ⁹ /L of 40 patients ≥ 30×10 ⁹ /L), 10 patients
Bleeding time	Prolonged 49 patients Normal in one patient.
Clotting time	Normal in all patients.
BM study	Increased number of megakaryocytes with left shift in all patients.
ANF & LE cell test	Negative (Done in all female patients)

Table-3. Particulars of patients who were in complete remission (CR).

Sl.no	Age	Sex	Duration of therapy	Initial PC	CR(PC)
1	20yrs	F	12 weeks	(< 30×10 ⁹ /L	230×10 ⁹ /L
2	26yrs	F	12 weeks	30×10 ⁹ /L)	280×10 ⁹ /L
3	25yrs	M	12 weeks	30×10 ⁹ /L)	180×10 ⁹ /L
4	20yrs	M	12 weeks	30×10 ⁹ /L)	190×10 ⁹ /L
5	15yrs	F	12 weeks	< 30×10 ⁹ /L	200×10 ⁹ /L
6	20yrs	F	12 weeks	< 30×10 ⁹ /L	300×10 ⁹ /L
7	24yrs	M	12 weeks	< 30×10 ⁹ /L	240×10 ⁹ /L

platelet count = PC.

Table-4. Age distribution of study patients.

Age in year	Total patients	percentage
21-40	28	56
15-20	16	32
More than 50	06	12

Table-5. Sex distribution of study patients.

Sex	Total patient	percentage
Female	30	60
Male	20	40

Discussion

This study provides to see the outcome of treatment with danazol of patients with chronic ITP refractory to prednisolone, azathioprine, vincristine or cyclophosphamide¹¹. Age of study population were between 15 – 55 years. 56% of the patient were belong to 21- 40 yrs & 32% were between 15- 20 yrs. 60% were female and 40% were male. Clinical presentation were purpura and brusie (100%), gum bleeding & epistaxis (80%), menorrhagia (50% of female patients), subconjunctival haemorrhage (30%), hematuria (20%). Two female patient had anemia with hemoglobin 6.4 gm/dl. One patient reported with visual impairment. In all patients of study platelet count had 30×10⁹/ L or less with large platelets in peripheral blood and bone marrow of all patients shown increased number of young megakaryocytes¹⁰. Antinuclear antibody (ANA) and LE cell (lupus erythematosus) test were negative in all patients. More than half of the refractory ITP patients improved by danazol⁸. Responses generally occur within 5 – 10 days much sooner than with azathioprine and

cyclophosphamide¹¹. Out of 50 patients 2 discontinued the therapy after 1st week and they were excluded from this study.

After starting of danazol on day 7, response rate was 79.2 % (platelet count raised in 42 patients out of 48). On 4th week follow up, 25% (12 patients) achieved (CR) complete remission (platelet count ≥ 1,50,000/cmm), 63.5% (30 patients) achieved (PR) partial remission (platelet count ≥ 50,000 - < 1,50,000/cmm) and 6 had no response at all. On 8th week, 7 patients remained in CR (37.5%), 5 in relapsed and remained in partial remission. 37.5% (7) patients remained in CR, 5 patient relapsed and remained in partial remission at 12th week of treatment.

Conclusion

Chronic ITP refractory to prednisolone & other drugs remains a serious problem all over the world. Splenectomy is the treatment of choice but our patient do not easily agreed to have splenectomy. Though danazol has limited benefit in chronic ITP but its prompt thrombocytosis effect, less toxicities and no carcinogenic effect make it more popular. Thus we can use danazol in chronic ITP patient refractory to prednisolone or others immunosuppressive agents.

References

1. Defeino SM, Lanchant NA, Kirhner JJ, Gottlich AJ: adult ITP. Clinical findings and response to therapy. Am.J.med,69:430,1980.
2. Jiji RM, Firozvi T, spurling CL: Chronic ITP. Arch Intern Med.132: 380,1973.
3. Monoharan A et al: slow infusion on Vincristine in the treatment of ITP. Am J hematomol 21: 135-138, 1986.

4. Brown DN, Elliot RHE. Refractory ITP successfully treated with cyclophosphamide. 215: 182, 1974.
5. Doan CA et al: Idiopathic and secondary thrombocytopenic purpura. Clinical study and evaluation of 381 cases over a period of 28 yrs. Ann intern Med. 53:861,1960.
6. Ahn ys et al; Vincristine therapy of idiopathic and secondary thrombocytopenia. New engl. J. Med. 1971: 376-380, 1974.
7. Carbon PP, Bono V , Frei E III et al : Clinical studies with Vincristine . Blood 21: 640-647, 1963.
8. Karause JR Et Al; ITP,. Development of acute nonlymphocytic leukaemia subsequent to treatment with cyclophosphamide, Med. Pediatr. oncol 10:61, 1982.
9. Borrows R, Kelton J: Fetal thrombocytopenia and its relation to maternal thrombocytopenia. New Engl. J. Med. 329;1463-1466,1963.
10. Garg SK, Amorosi EL, Karpatkin S; Use of the megathrombocyte as an index of megakaryocyte number. N.Engl. J. Med. 283; 11-17, 1971.
11. Ahn YS, Harrington WJ; Treatment of ITP, Annu rev. Med.28;299-309. 1977.
12. Schreiber AD et al; Effect of danazol in immune thrombocytopenic purpura. N.Engl.j. Med 316;503, 1987.
13. Meyers NC et al; Results of treatment in 71 patients with ITP . Arch inter. Med.sci 242;295,1961.

All correspondence to:
M Rafiqzaman Khan
 Deputy Chief Medical Officer
 Rajshahi University Medical Centre
 Rajshahi.