Original Article

A Study from Eastern India on the Role of Dapsone Therapy in Patients of Persistent and Chronic Immune Thrombocytopenia; Where Do We Stand ?

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Background : Immune thrombocytopenia (ITP) is a heterogeneous disorder and remains a diagnosis of exclusion of other causes of thrombocytopenia. Even though response to first line therapy is around 75-80%, almost 60-70% of adult patients experience relapse. Dapsone, first described as potential therapeutic agent for ITP since 1988, with a response of 29-63%.

Material and Method: This Prospective interventional study was conducted on 50 persistent and chronic ITP patients. Dapsone was given orally at a dose of 2mg/kg/day; followed up for 12 months. Response evaluated as per published guidelines.

Result : Out of total 50 patients, 36(72%) were female. Patients with persistent and chronic ITP were 15(30%) and 35(70%) respectively. Non-responders were withdrawn from the study at the end of 6 months. At the end of 12 months, complete response found in 10(20.8%) patients.

Conclusion : It is a very cheap drug; evaluation of its role in safety and efficacy help us to reduce the treatment burden in developing countries like India. No predictors of response were found. The major difference in the response in our study compared to previous studies need to be clarified further with large sample size.

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Key words **: Immune Thrombocytopenia, Persistent And Chronic, Dapsone Therapy, Response.**

The incidence of ITP is 0.2-0.4 new cases per 10,000/year in adults and 0.2-0.7 per 10,000/year in children and can be an isolated primary condition or it may be secondary to other conditions[1,2]. Out of all, 80% are primary ITP. Likelihood of spontaneous remission from ITP is age related, with 1-year remission rates of, 74% in children from 1 year of age, 67% in those between 1 to 6 years and 62% in 10 to 20 years of age[3]. Natural history data in adults are less well studied, with reports of 20% to 45% of patients achieving complete remission by 6 months[4]. Sustained response to steroids, intravenous Immunoglobulin (IVIg) and anti-D noted in approximately two third of patients. Rituximab used as second line therapy, shown response rate of 40%. Thrombopoeitin Receptor agonists have well established efficacy and safety; but these are very costly and risk of infection is high. Splenectomy is curative for chronic ITP with a response rate of 66-88%; relapse rate of 15%. But not preferred due to risk of surgery, thrombosis and infection.

Editor's Comment :

- Diagnosis of Immune thrombocytopenia (ITP) remains a diagnosis of exclusion of other causes of thrombocytopenia.
- Though response to first line therapy is around 75-80%, almost 60-70% of adult patients experience relapse.
- Dapsone used in chronic and persistent ITP with reported response rate of 29-63%, is a very cheap drug.
- Evaluation of its role in efficacy and safety help us to reduce the cost of treatment burden in resource constraint countries like India.

Dapsone is used in ITP at an oral dose of 1–2 mg/kg daily; rapidly and completely absorbed with peak drug levels being achieved within 4-8 hours of intake. Excretion of the drug is mainly through urine and a constant blood level can be maintained with regular daily dosing. The elimination half-life is estimated to be 30 hours[5,6]. There is no clear explanation of how it helps in the treatment of ITP, although some argue that excessive red cell destruction by Dapsone blocks the reticuloendothelial system[6]. However, in many patients treated with Dapsone, there is no significant drop in hemoglobin levels, and some remain in remission even after the drug is discontinued[7]. It is well tolerated drug, with minimal adverse effects mentioned in literature. It causes hemolysis in patients

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with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency; thus mandatory to check G6PD assay before starting Dapsone. There are cases of hemolysis noted in patients with normal G6PD assay. Cases of itching, Steven Johnson Syndrome and also hepatitis noted in few studies[7].

Materials and Methods

This was a prospective interventional study conducted over a period of two years from January, 2018 to December, 2019. Patients aged between ≥3 years to ≤60 years with features of bleeding manifestation were included in the study after getting informed consent and diagnosed as persistent and chronic ITP as per American Society of Hematology (ASH) 2011 guideline[8,9]. Patients aged >18 years were considered as adults those with age ≤18 years as children (age corrected to the nearest whole number). A detailed history was taken along with clinical evaluation of all the patients. Clinical history and physical examination was done in all patients meticulously. The severity of bleeding graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)[10].

Inclusion criteria:

Patients included in the study fulfilled all the following criteria-

(a) age ≥3 years to ≤60 years,

(b) Diagnosed case of Persistent and Chronic ITP,

(c) Platelet count<30×10^9/L or,

(d) Platelet count <50×10^9/L with bleeding manifestation.

Exclusion criteria :

(a) Patients with secondary ITP patients, pregnant patient or lactating mother,

(b) Earlier treated with splenectomy, with active severe infection or history of severe infection within 4 weeks before inclusion,

(c) Patients who are allergic to sulfonamides, patients with history of methemoglobinemia, G6PD deficiency (screening done by methemoglobin reduction test in both sexes),

(d) Patients with hemoglobin level<8.0 gm/dl and/or neutrophil count<1.5x10^9/L,

(e) Patients with history of autoimmune or hereditary haemolytic anemia

(f) And, patients with impaired liver or kidney function.

Rescue medications (dose increment of steroid or IVIg) required in 21 patients. Patients were on various dosage of steroid, tapering was started from 8 weeks after addition of Dapsone. Gradual tapering of steroid was done over a period of 8 weeks. Complete Blood Count (CBC), Liver Function Test (LFT), urea, creatinine were assessed periodically.

Response evaluation: Responses were assessed as per "ASH-2011 Evidence based practice guidelines for ITP"[9]:-

- ***Complete response :*** Platelet count of 100×10^9/L or more, measured on two occasions, 7 days apart and the absence of bleeding without rescue medication.
- ***Response :*** Defined as platelet count of 30×10^9/L or more and at least a doubling of baseline platelet count measured on two occasions, 7 days apart.
- ***No response :*** Less than 30 × 10^9/L or less than 2 fold increase in the platelet count or with bleeding manifestation. Measured on more than one occasion, one day apart.

Criteria used for non-responders: Platelet count at the end of the study is <30 x 10^9/L, but also, during the study period if:

- They need a rescue therapy, 6 weeks after inclusion.

or

- They receive any other second line therapy.

Patients not responded even after 6 months (this time period was taken as our patients were on overlapping steroid for 16 weeks), were withdrawn from study, and treated with other therapeutic modalities.

Statistical Analysis: Quantitative values were reported as median (1st-3rd interquartile) and qualitative data as percentage. P-values were derived using Chi square test and Mann-Whitney test for qualitative and quantitative values, respectively. Wilcoxon matched pairs test was used to compare platelet count before and after treatments. $P<0.05$ was considered significant. Statistical analyses were performed with STATATM Software (Stata Corp).

Results

Out of 50 patients, 36(72%) were female. Median age was 20 years (range,3-60 years). These included 26(52%) children≤18 years and 24(48%) adults >18 years. Fifteen(30%) patients diagnosed as persistent ITP and 35(70%) has chronic ITP. All the patients were treated with steroid and IVIg previously. Duration of symptoms before starting dapsone was 4-32 months. Twenty four(48%) patients had grade1, 22(44%) patients had grade 2 and four(8%) had grade3 bleeding manifestation as per NCI-CTCAE criteria.10 There was petechiae and purpuric spots in 45(90%) patients, wet purpura in 21(42%) patients, epistaxis in 21(42%) patients, menorrhagia in 13(26%) patients and gum bleed in 11(22%) patients. The median platelet count

of total cases at diagnosis was 13x109/L (2-20x109/L) in both adults and children. Summary of the cohort (n=50) represented by CONSORT flow diagram in Fig 1. Two patients were withdrawn from study at the beginning (one due to itching with rashes, other patient due to severe bleeding requiring other mode of therapy).

Disease duration prior to Dapsone ranges from 4-32 months. Unable to afford for costly medicines and various complications with splenectomy, patients were continued with steroid in various doses. Steroid was continued till 8 weeks, and gradual tapering was done. Dapsone was administered at the dose of 2 mg/kg/day, responses evaluated periodically. As shown in Fig 2, response at 2 months was 72.9%, while the patient was on steroid. After omission of steroid, response rate reduced to 37.5% at the end of 6 months. At the end of 12 months only 10 (20.8%) patients were maintaining the platelet count.

Out of 36 female patients, ORR noted in 8 (22%) patients and out of 14 male patients ORR noted in 2 (14%) patients. Subgroup analysis of patients (n=15) with persistent ITP, ORR noted in 4 (27%) patients; response in 3 (20%) patients, CR noted in 1 (7%) patients. Patients (n=33) with chronic ITP, ORR noted in 6 (18%) patients; response in 5 (15%) patients, CR in 1(3%) patient. Subgroup analysis of response in children (n=25) ORR in 8 (32%) patients, out of which CR noted in 6 (24%) patients. Adult (n=23) cohort showed, ORR in 2 (8.7%) patients, none of the patients in CR.

Most patients (n=46) tolerated the therapy well. As shown in Fig 3, severe side effects noted in two patients; intractable itching with rashes in one patient and fall in hemoglobin (2.4 gm/dl) noted in other patient. Mild to moderate adverse effects seen in 46% patients; 10% patients complained of nausea, symptoms subsided with oral antiemetic and lifestyle modification. None of the patient warrants dose modification. Six percent patients were complaining of mild itching. Headache was seen in 7% patients, relieved with analgesics. Deranged LFT (less than 3 fold increments in AST/ALT) found in 13% patients, therapy continued with weekly once follow up. Significant fall in hemoglobin (>1.0gm/dl) noted in 6 patients. Out of 10 responded patients, fall in Hb (>1.0gm/dl) noted in only three patients.

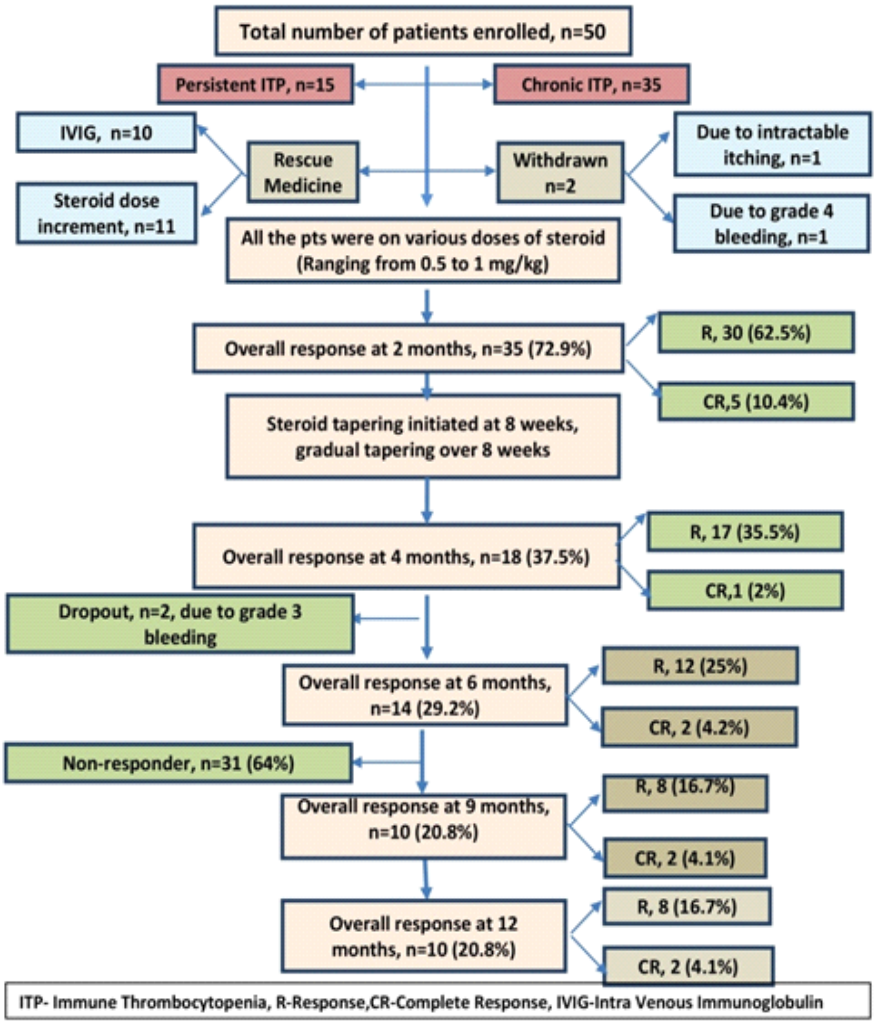

Fig 1 — The CONSORT flow Diagram of the cohort included in the study (n=50)

Discussion

In contrast to published literature[2,3,4], in the present study, pediatric population is high, possibly due to more number of younger populations in India, and also it may be due to the fact that in younger population there is a chance of getting more medical attention than elder population in developing countries like India. Response rate is better in pediatric population, but there is no statistical difference (p=0.103)

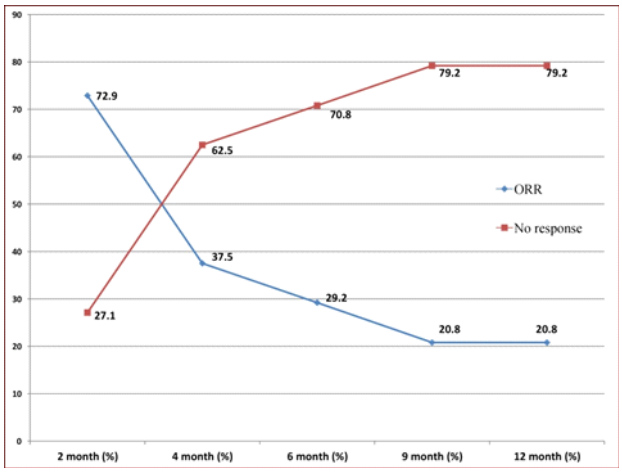

Fig 2 — Comparing response at various time points in total cohort

matching the literature.

In the present study, female population was more (72%) in all age groups. An association between female gender and increased risk of chronic ITP was found in majority of studies[4,7,11]. However some of the studies on childhood ITP reported a slightly higher preponderance in boys,[11-13] while others found an equal age distribution[14]. At the end of 12 months, no statistical difference in response noted as per gender (p=0.81). As per phase of ITP, Dapsone response, no statistical difference were found between the persistent and chronic ITP patients (p=0.70).

Duration of disease at the time of entry into the study ranges from 4 to 32 months and most of the patients were on various doses of steroid. Khan YB et al15 from Jammu and Kashmir, India also conducted a similar study in 100 ITP patients, mean interval between diagnosis and start of Dapsone was 2 years

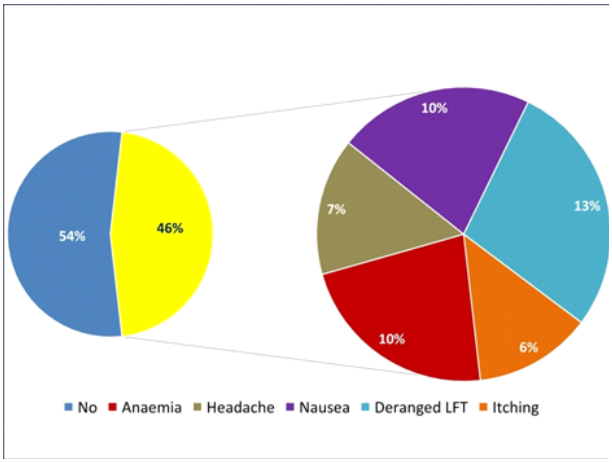

Fig 3 — Side effects profile with Dapsone therapy [includes mild and moderate adverse effects noted in 46% of the study population. Severe adverse effects found only in two (4%) patients]

similar to present study. Duration of disease doesn't have any effect on therapy response. Platelet at diagnosis was not found to have any impact in response outcome.

Response at the end of two months was noted in 35 (72.9%) patients, at this point of time patients were on both steroid and Dapsone. In the study by Khan YB *et al*[15], the mean time to onset of response was 21 days (range, 8 - 97). Maximum response was noted at two months in our cohort. But the exact time of action could not be assessed because patients were on Dapsone and overlapping steroid. This combination was continued for two months, because most of the studies had shown variable response duration ranging from 9-260 days. Most of the studies were done as Dapsone monotherapy without steroid overlapping except one such published in the year 2017 by Cle´mentine E *et al*[16] In the said study[16], patients received prednisone at a median dose of 1 mg/kg/day and was discontinued after a median duration of 28 days (21–37.5). Response is better in patients with steroid and Dapsone compared to Dapsone monotherapy. Steroid sparing effect of dapsone is proven in Leprosy, but not in ITP. This role of Dapsone has to be evaluated further in large trail. In future that may help us to reduce the side effects of prolonged, high dose use of steroid.

At the end of 6 months, we found that overall response maintained in only 14 (29.2%) patients, out of which response noted in 12 (25%), complete response noted in 2 (4.2%) patients. At the end of 9 months another 4 patients had shown loss of response with relapse of disease. This response is maintained at the end of 12 months. ORR at the end of 12 months were 20.8%, compared to other studies (as shown in Table 1) the response rate was very less. All our patients were having good compliance to therapy and on regular follow up; still very low level of response as compared to others which we can't explain.

In the reports by Cle´mentine E *et al*[16] steroid given over a period of 28 days; then tapered suddenly; response noted with Dapsone monotherapy in 47.4%(n= 9/19 patients) with a CR of 21.1%(n=4/19) and a PR in 26.3%(n=5/19). But, in the present study, even after slow tapering of steroid over 4 weeks, response to dapsone was poor. Almost 78% of patients at the end of 6 months required other treatment modalities to manage the bleeding manifestation.

In the present study, patients achieved response in 8 (16.7%) patients, compared to CR only in 2 (4.1%). Study by Patel AP *et al*[17] using an average dose of dapsone of 1.57 mg/kg/day showed mean time

Table 1 — *Comparison of the results from present study with different other studies*

Parameters	Godeau *et al*[20]	Damodar *et al*[7]	Vancine-Califani *et al*[21]	Zaja F *et al*[18]	Patel AP *et al*[17]	Khan YB *et al*[15]	Clementine E *et al*[16]	Present study
Year of study	1993	2005	2008	2012	2014	2014	2017	2019
Type of study	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Prospective
No of patients	66	90	52	20	38	100	42	50
Median age (years)	48	20.6(3-61)	38(13-78)	51(27-74)	29.5(20-68)	36	57.1(34-77)	20(3-60)
Median platelet count before Dapsone 10^9/L	NA	13.2	NA	19	12	8000	14(6-22)	13
Complete response/ response	NA/50%	48.9/63.3%+	NA/44.2%	20%/55%	40.5%/48.5%	NA/47.7%	38.1%/16.7%	4.1%/ 16.7%
Time to response in days	21(8-90)	105(30-270)	-	30(15-60)	59(27-108)	21(8-97)	29(24-41)	-
Relapse during Dapsone therapy	1/20(5%)	NA	NA	0	2/18(11.1%)	0	6/23(26.1%)	38/50(76%)
Withdrawal due to toxicity n(%)	7/66 (10.6)	3/90 (3.3)	1/52(1.9)	1/20(5)	2/38(5.3)	0	9/42 (21.4)	1/50(2%)
Average dose	75-100 mg/day	2.15 mg/kg/day	100 mg/day	50-100 mg/day	1.57 mg/kg/day	1-2 mg/kg/day	33.3-100 mg/day	2 mg/kg/day
Average treatment duration in responders (m)	12.5	9 (PR)-12.5(CR)	9.7	31	10	5 years	9.7	12

NA = not available, y = years, m = months

to response of 57 days (range, 19-108 days). The response rate was 48.6% (complete response = 40.5%). They concluded that, response to dapsone is slow, sustained, and relapses are uncommon on therapy but, it's withdrawal leads to relapse in most cases. Damodar S *et al*[7] observed response rate of 63.3% (CR in 48.9%). Zaja F *et al*[18] reported response in 55% cases with CR of 20%. They used Dapsone at a lower dose (100mg OD, average weight: 77kg, range: 57–100kg) in comparison to the present study (2mg/ Kg/Day) and Dapsone was discontinued if there was no response after two months.

The major difference in the response in our study compared to other studies need to be clarified further with large sample size. Study by Patel AP *et al*[17] had shown that time to response and peak response was noted in 57 days and 155 days respectively. This study highlighted the very late cumulative response with Dapsone. The non-responder patients in the present study were withdrawing from the study at the end of 6 months. It needs to be studied further to prove whether prolonging therapy beyond this period have any effect in increasing response to the therapy.

In a very recently published review article by Matzdorff A *et al*[19] have shown that, therapeutic response may be slow and an effect is usually to be expected after 4-6 weeks but have well established safety profile. There was no significant difference in the mean fall in haemoglobin level between responders and non-responders 1.0gm/dl (range, 0.4–2.0) *versus* 1.8gm/dl (0.9–2.5) respectively (p=0.16). This gives an idea that mechanism of action of Dapsone, may not due to the destruction of Red Blood Cells (RBCs) in reticuloendothelial system and sparing platelets. The major difference in the response in our study compared to other studies need to be clarified further with large sample size.

Limitations of the study:

- Small sample size
- Shorter period of study including follow up
- Long term adverse effects could not be studied

Conclusion

At the end of 12 months, only 20.8% patients were maintaining the platelet count. Though dapsone is cheap, safe and well tolerated drug in all age group of patients but, it's long term response rate (especially complete remission, 4.1%) is not encouraging and relapse is substantial.

Ethics approval : The study was approved by the institutional ethical committee

Source of Funding : None

Conflict of interest : No Conflicts of Interest declared by any author

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