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Original Article

Use of Dapsone in Chronic/Refractory Immune Thrombocytopenic Patients: A Single Center Experience

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ABSTRACT

Background Dapsone is a second-line therapy for immune thrombocytopenia (ITP). It is cost-effective, with a response rate comparable to other drugs used as second-line therapy, such as azathioprine, danazol, cyclophosphamide, cyclosporine, vincristine, rituximab, and eltrombopag.

Material and Methods This retrospective study analysed ten adult patients who presented to our hematology division outpatient clinic between March 2013 and July 2021, was diagnosed with chronic/refractory ITP, did not respond to first-line therapy, and used dapsone.

Results Eight (80%) patients were female, and 2 (20%) were male. The median age was 50 (range, 24-64) years. The mean pre-treatment platelet value was $12.8x10^9$/L (range: 4-22.1x109/L). The median duration of symptoms before dapsone treatment was 60 (6-360) months. The median number of treatments received before dapsone was 4 (range: 3-6). All patients were routinely treated with oral dapsone 50 mg for two weeks, followed by 100 mg. The median time to treatment response was 39 (range: 14-90) days. The response rate was 60% (complete response 40%, partial response 20%). Asymptomatic anaemia was observed as a side effect in only one patient.

Conclusions Based on these results, it can be speculated that dapsone is an effective, inexpensive, and well-tolerated treatment option. Considering the economic status of developing countries, it seems very attractive to use dapsone as the second-line therapy for chronic/refractory ITP. To the best of our knowledge, this is the first study in Turkey on the use of dapsone for chronic/refractory ITP.

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INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disease characterised by low platelet count and mucocutaneous bleeding. Patients diagnosed with ITP are classified into three categories: acute ITP (<3 months), persistent ITP (3-12 months), and chronic ITP (>12 months).[1] Life-threatening bleeding is rare in ITP (0.16%-0.38% in adult patients) and is mostly observed in elderly patients. Steroids are the main drug used in first-line therapy. Seventy per cent of adult patients respond to steroid therapy, of whom 50% showed sustained response after treatment discontinuation.[2] The other half of the patients either do not respond to steroids or become steroid dependent. Treatment options for these patients include pulse dexamethasone, azathioprine, cyclosporine, danazol, or vincristine, with response rates ranging from 10% to 30%, and splenectomy, to which approximately 70% of the patients respond.[2] New treatment options such as rituximab or thrombopoietin receptor agonists (TPO-RA) are promising in patients with contraindicated splenectomy.[3] The high cost of these drugs and their side effects, such as thrombosis and bone marrow reticulin fibrosis, should be considered in the long-term use of TPO-RA.[4] Dapsone (4,4-Diaminodiphenyl sulfone) is an antibiotic from the group of sulfones as well as a folate antagonist with anti-inflammatory and anti-parasitic effects. It is also used for the treatment of leprosy. Since it is both inexpensive and well tolerated, it is a good option for second-line therapy.

A response rate of 62% was achieved in 21 steroid-dependent patients reported to be using dapsone for the first time in ITP.[5] A response rate of 50% was also reported in a case series of 66 patients.[6] Similar rates were found in another reported publication.[7] The mechanism of action of dapsone in ITP is not fully understood. One possible mechanism is the induction of hemolysis due to the conversion of dapsone to hydroxylamine, which leads to erythrophagocytosis in the reticuloendothelial system. Thus, sequestration and destruction of platelets are prevented. Another hypothesis is that dapsone is an immunomodulatory drug.[8] Methemoglobinemia and hemolysis are the most common side effects of dapsone therapy. Other rarer side effects may include peripheral neuropathy, agranulocytosis secondary to bone marrow suppression, hepatitis, dermatitis, and psychosis. Response to dapsone is slow, sustained, and on treatment, relapses are rare. Because of the slow response to treatment, patients should be treated for at least three months. There is no consensus on when to discontinue dapsone therapy. Most patients develop relapse after the discontinuation of dapsone. The present study retrospectively evaluated our patients on dapsone, considering that it may be an option in chronic/refractory ITP due to its acceptable response rates, side effect profile, and cost advantage.

MATERIAL AND METHODS

The study included ten patients who were followed up in the Adult Hematology Outpatient Clinic of Bursa Uludag University Faculty of Medicine Hospital, diagnosed with chronic/refractory ITP between March 2013 and July 2021, and used dapsone as second-line therapy. The data of patients were obtained from the hospital information system and patient files. Patients under the age of 18 and patients with acute ITP were not included in the study. Haemoglobin and platelet levels at diagnosis, age at diagnosis, number of lines of treatment received before dapsone, duration of dapsone therapy, treatment responses, and treatment complications of all patients were evaluated. All patients were initiated on oral dapsone 50 mg/day for two weeks. The dose was increased to 100 mg after that. Conditions such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), H. pylori, systemic lupus erythematosus (SLE), and lymphoma that may cause secondary thrombocytopenia were tested and excluded. Bone marrow biopsy was performed in patients with an indication.[9] A platelet count ≥30,000/μL or twice the baseline and no signs of bleeding were defined as the response. A platelet count greater than $100x10^9$/L was considered a complete response.[10] The study was approved by Bursa Uludag University's local ethics committee.

RESULTS

Ten patients receiving dapsone were previously treated with at least three lines of treatment (steroid, intravenous immunoglobulin, splenectomy, danazol, rituximab, etc.). Splenectomy was the most common treatment in the second line (40%) (Figure 1). The data of 10 patients and their response to dapsone therapy are shown in Table 1. All patients were initiated on steroid therapy as the first-line treatment. Intravenous immunoglobulin was administered to 8 patients who had bleeding or an emergency such as surgery (80%). Although there are treatment options such as cyclosporine, cyclophosphamide, and vincristine for the second-line treatment, these agents were not

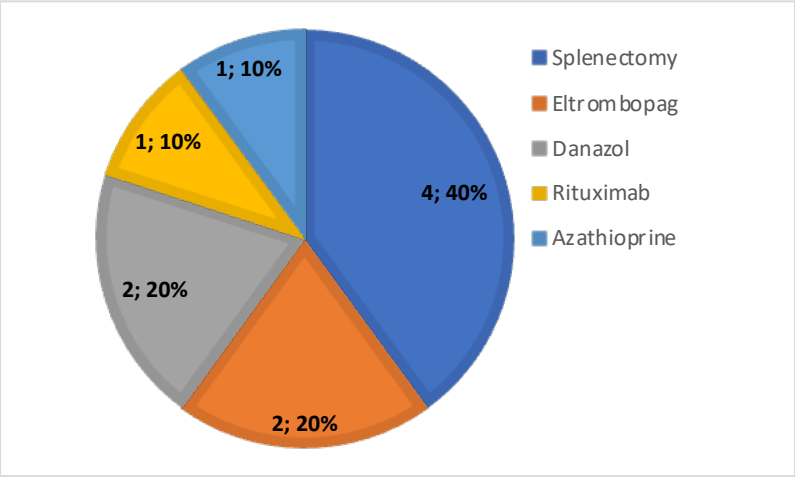

Figure 1. Treatments of choice as second-line treatment in patients with chronic/refractory ITP.

administered to the patients. Despite the absence of any side effects, dapsone therapy of one patient was discontinued in a short period of 1.5 months since their platelet count did not increase. Response status could not be evaluated in another patient due to loss of follow-up during dapsone therapy.

Of the patients, eight were female (80%), and two were male (20%). The median age was 50 (range: 24-64) years. The pre-treatment mean haemoglobin and platelet values were 12.6 g/dL (range: 9.1-16.4) and 12.8x10^9/L (range: 4-22.1), respectively. The median duration of symptoms before dapsone was 60 (range: 6-360) months. The median follow-up period of the patients was 6 (range: 2-29) months (Table 2). The initial admission complaint was bleeding findings (nasal, gingival, and subcutaneous). Severe bleeding findings such as intracranial haemorrhage were not observed in any patients. Asymptomatic anaemia was observed in only 1 (10%) female patient as a side effect during dapsone therapy (from 12.3 g/dL to 8.8 g/dL). This side effect was noted during the routine tests performed during the second week of the treatment.

Seven of the ten patients diagnosed with chronic ITP underwent bone marrow biopsy. Their pathology reports revealed that six patients had increased megakaryocyte count, while one had decreased

Table 1. Patients' data and response to dapsone therapy.

Patient number	1	2	3	4	5	6	7	8	9	10
Age/gender	39/M	55/F	24/F	30/F	50/M	31/F	64/F	60/F	57/F	48/F
Disease duration before dapsone (months)	12	360	168	180	NA	6	60	8	24	84
Previous treatments										
Steroid	+	+	+	+	+	+	+	+	+	+
Immunoglobulin	+	+	+	+	-	+	-	+	+	+
Splenectomy	+	+	+	+	+	+	+	+	-	+
Danazol	+	-	+	-	+	+	+	+	-	-
Azathioprine	+	-	-	+	+	-	-	-	-	-
Cyclosporine	-	-	-	-	-	-	-	-	-	-
Cyclophosphamide	-	-	-	-	-	-	-	-	-	-
Vincristine	-	-	-	-	-	-	-	-	-	-
Rituximab	+	-	+	+	+	-	-	-	-	+
TPO-RA	+	+	+	+	-	-	-	-	+	+
Pre-dapsone platelet count (x10^9/L)	10.3	5.15	13.5	13	NA	22.1	15.4	4	17	15.4
Duration of treatment (months)	6	3	17	1.5	NA	6	NA	25	3	24
Response[a]	Yes	No	Yes	No	No	Yes	NA	Yes	Yes	Yes
Complete response[b]	Yes	No	Yes	No	No	Yes	NA	No	No	Yes

a platelet count ≥30x10^9/L as response; b platelet count ≥100x10^9/L as complete response.
TPO-RA: thrombopoietin receptor agonist; NA: not available.

Table 2. Characteristics of ten patients on dapsone.

Median age (years)	50 (24-64)
Gender (M/F)	2/8
Hemoglobin (g/dL)	12.6 (9.1-16.4)
Platelet count (10^9/L)	12.8 (4-22.1)
Median duration of symptoms before dapsone (months)	60 (6-360)
Median follow-up (months)	6 (2-29)

Table 3. Results of dapsone therapy.

Complete response n (%)	4 (40%)
Response n (%)	6 (60%)
Non-response n (%)	3 (30%)
Not evaluated n (%)	1 (10%)
Relapse n (%)	5 (83.3%)
Time to response (days)	39 (14-90)
Treatment duration (months)	6 (3-25)
Response time after discontinuation of dapsone therapy (months)	3.5 (1-12)
Number of patients with sustained response at 6 months after discontinuation of dapsone	1 (10%)

megakaryocyte count. The median time to respond to dapsone therapy was 39 (range: 14-90) days, and the median duration of treatment was 6 (range: 3-25) months. While six patients responded to dapsone therapy, 4 had a complete response (>10 x109/L). Four of the six patients who had a response developed a relapse in the first six months after discontinuing dapsone therapy, and one patient developed a relapse at 12 months. One patient is currently on dapsone therapy (>25 months). The median duration of response was 3.5 (range: 1-12) months after discontinuing dapsone therapy. Only one patient had a remission period of more than six months after treatment discontinuation (Table 3).

Patient number one was reinitiated on dapsone therapy after relapse. A response was regained with this treatment. The patient, who received dapsone therapy for seven months as the initial treatment and remained in remission for 12 months after treatment discontinuation, was given treatment for the second time for 12 months. While the response was maintained during the follow-up of the patient whose treatment was discontinued, the patient developed a soft tissue infection in the surgical site associated with aseptic necrosis of the femoral head and died after two days of follow-up at intensive care due to septic shock secondary to this infection. The patient's dapsone therapy dose, duration, and response are shown in Figure 2.

DISCUSSION

The response to dapsone therapy is usually slow. Administering treatment for at least three months is recommended to see the treatment response. Two patients (20%) responded on day 14 and the others on days 39, 45, 70, and 90, respectively. The median response time was 39 (14-90) days. The study by

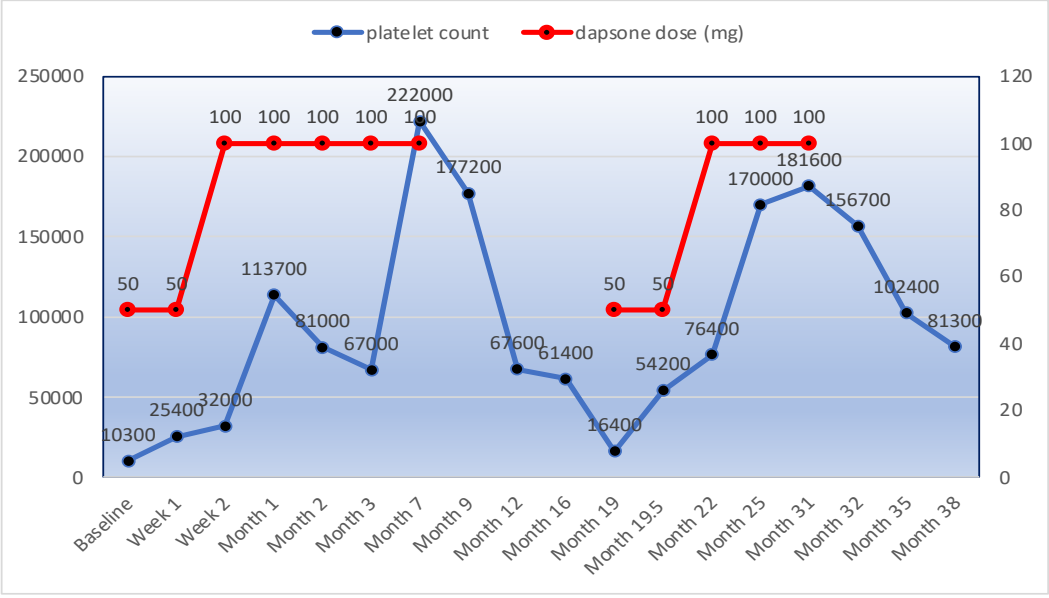

Figure 1. Relationship of a platelet count of patient number one with dapsone dose and duration.

Table 4. Summary of studies on dapsone therapy in patients with ITP.[15]

Reference number	Durand et al.[15]	Godeau et al.[5]	Hernandez et al.[17]	Godeau et al.[6]	Damodar et al.[13]	Vancine et al.[18]	Zaja et al.[11]	Present
Country	France	France	Spain	France	India	Brazil	Italy	Turkey
Number of patients	5	21	15	66	90	52[a)]	20[b)]	10
Median age (years)	76 (68-87)	37 (22-79)	58 (16-84)	43 (26-68)	21 (3-61)	38 (13-78)	51 (27-74)	50 (24-64)
Disease duration before dapsone (months)	34 (6-60)	14 (2-240)	29 (12-131)	52 (3-240)	CR: 21 (6-120) PR: 31 (6-84) NR: 25 (6-120)	R: 6 (1-21) NR: 5 (1-30)	46 (3-274)	60 (6-360)
The median number of treatments before dapsone	2 (0-4)	2 (1-9)	1 (1-2)	3 (0-10)	NA	NA	NA	4 (3-6)
Mean platelet count before dapsone ($x10^9$/L)	36 (23-43)	16 (2-49)	16 (7-48)	23 (2-49)	CR: 18 (1-49) PR: 13 (2-35) NR: 10 (2-46)	R: 26±14 NR: 18±11	19 (NA)	12.8 (4-22.1)
Daily dapsone dose	75 mg	100 mg	100 mg	100 mg	1-2 mg/kg	100 mg	100 mg	100 mg
Median duration of treatment, months	14 (2-48)	3 (1-11)	6 (1-31)	R: 13 (1-48) NR 3 (1-9)	CR: 13 (3-18) PR: 9 (3-14) NR: 6 (3-8)	R: 39 (1-91) NR: 3 (1-29)	9 (4-56)	6 (2-29)
Response rate[c] (%)	100	29	40	50	63	44	55	60[d)]
Combination therapy	No	Yes	No	Yes	No	No	No	No

[a] Forty patients with a diagnosis of primary ITP.
[b] Sixteen patients with a diagnosis of primary ITP.
[c] A platelet count ≥50,000/μL was considered a response to dapsone.
[d] A platelet count ≥30,000/μL was considered a response to dapsone in our study.[6]
CR: complete response (>$10x10^9$/L), ITP: immune thrombocytopenia, NR: non-responder (<$5x10^9$/L), PR: partial response (5-$10x10^9$/L), R: responder (>$5x10^9$/L), NA: not available.

Zaja *et al*.[11] reported a mean time to response of more than one month. While the response to danazol and azathioprine, the other second-line treatment options, is slow, the response to cyclophosphamide, cyclosporine, vincristine, splenectomy, rituximab, and thrombopoietin receptor agonist (TPO RA) eltrombopag is faster.[9]

Anaemia may develop secondary to bleeding in most patients with ITP. Since dapsone will induce hemolytic anaemia in glucose-6-phosphate dehydrogenase (G6PDH) deficiency, the level of the G6PDH enzyme in male patients using this drug is a parameter that should be checked before treatment. In our study, two male patients received dapsone. Although the G6PDH test was not performed before treatment, low haemoglobin levels were not observed in these patients. Dapsone may rarely reduce haemoglobin oxidation by inhibiting the haemoglobin reductase enzyme in erythrocytes. Side effects such as toxic hepatitis, anaemia, and skin lesions may be seen in patients using dapsone.[10] The acceptable safety profile of dapsone has been previously reported in several articles.[9,11-13] Several studies have reported that dapsone is an effective drug regardless of previously used treatments. The study by Zaja *et al*.[11] in 20 patients reported a response rate of 55% and a complete response rate of 20%, Damodar *et al*.[13] found a response rate of 61.8% and a complete response rate of 48% in 55 patients, and Colella *et al*.[14] reported a response rate of 66% and a complete response rate of 24% in 122 patients. The results of our study revealed a response rate of 60% and a complete response rate of 40% in 10 patients.

A few studies are performed to determine the duration of response after discontinuation of dapsone therapy. Godeau *et al*.[6] reported that 1 out of 13 patients who responded to dapsone therapy had a sustained response, and Patel *et al*.[10] said that 2 out of 18 patients with treatment response had a sustained response. Zaja *et al*.[11] reported that 1 out of 20 patients who responded to treatment had a sustained response for more than six months after discontinuing the drug. In our study, 1 of the six patients with a response had a more than six months response duration. There is a need for studies with more significant numbers of patients to understand better the response time after discontinuing dapsone therapy. The study published by Lee *et al*.[15] summarised the results of different numbers of patients from other countries diagnosed with chronic ITP and treated with dapsone. All

analyses were conducted with a few patients (Table 4). Table 4 shows that the dapsone dose was generally 100 mg orally in those studies, as in our study. A notable detail in this table is that Godeau *et al*.[6] used dapsone and danazol combination therapy in some non-responders. In the study of Rattanathammethee *et al*.[17], dapsone was administered with colchicine therapy to patients with chronic/refractory ITP. In the present study, we did not administer a combination therapy to any patient. Moreover, as is seen in this table, a platelet count ≥50,000/μL was considered a response to dapsone therapy. We, however, considered a platelet count ≥30,000/μL as a response to dapsone.

CONCLUSIONS

In conclusion, using dapsone as second-line therapy is appealing for several reasons. Among these are its cost-effectiveness and comparable efficacy with other drugs used as second-line treatment options, such as azathioprine, cyclosporine, vinca alkaloids, mycophenolate mofetil, cyclophosphamide, danazol, rituximab, and eltrombopag. Dapsone has a good safety profile and rarely requires discontinuation due to side effects. Discontinuation of dapsone therapy, as with the TPO agonist eltrombopag, leads to relapse in many patients. Although the TPO agonist has a high response rate, its higher cost is a disadvantage. In contrast, the cost of treatment with dapsone is considerably low. Considering the economic status of developing countries, it seems very attractive to be used as second-line therapy for ITP. As an oral agent, dapsone provides an option in cases of ITP with no response after steroid and splenectomy. Considering its tolerability, it should be considered for refractory ITP patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

Ethics approval was obtained from the non–invasive clinical research ethics committee of the medical faculty (date: 08.12.2021, number: 2021-18/28). All aspects of the study, including periodical clinical and laboratorial checkups, were performed according to the principles of the declaration of Helsinki (64th, 2013).

Authors' Contribution

Study Conception: ÖC, VÖ, TGK; Study Design: ÖC, VÖ, FÖ, TE; Supervision: ÖC, TZT, FÖ; Literature Review: ÖC, VÖ, FÖ, TE; Critical Review: ÖC, FÖ, VÖ; Data Collection and/or Processing: ÖC, FÖ, VÖ, VA; Analysis and/or Data Interpretation: ÖC, VÖ, FÖ, TE; Manuscript preparing: ÖC, VÖ, FÖ.

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