BLOOD RESEARCH
VOLUME 52 · NUMBER 2
June 2017
ORIGINAL ARTICLE

Dapsone therapy for refractory immune thrombocytopenia patients: a case series

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p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2017.52.2.95
Blood Res 2017;52:95-9.

Received on December 10, 2016
Revised on March 1, 2017
Accepted on April 11, 2017

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Background
Dapsone has been recommended as a second-line immunosuppressive agent for patients with immune thrombocytopenia (ITP).

Methods
We retrospectively analyzed the efficacy and safety of dapsone therapy in patients with ITP.

Results
Nine ITP patients were treated with dapsone at a dose of 50–100 mg/day between May 2013 and March 2016. All patients were refractory to multiple previous treatments, with a median of 7 agents (range, 4–8), and 3 patients had undergone a previous splenectomy. The median pre-treatment platelet count was 4×10^9/L (range, $3–27\times10^9$/L). Only 1 patient (11.1%) responded to dapsone therapy. No severe adverse events were observed, except for 1 case of dapsone hypersensitivity syndrome.

Conclusion
Although dapsone is still useful for some patients, it may be ineffective in heavily pretreated patients with profound thrombocytopenia.

Key Words Immune thrombocytopenia, Dapsone, Efficacy, Toxicity

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune hematologic disease that results from antibody-mediated destruction of platelets, and impaired platelet production [1, 2]. Bleeding and infection contribute to morbidity and mortality in ITP patients, and the treatment for adults with ITP who are unresponsive to, or who experience relapse after, initial corticosteroid therapy remains a challenge [3]. Although splenectomy has been the standard second-line treatment, physicians and patients are increasingly averse to splenectomy and as such, a reduced splenectomy rate has already been observed in previous studies [4-6]. New therapeutic options such as rituximab or thrombopoietin-receptor agonists (TPO-RAs) offer promising alternative management of ITP [7]. However, their use remains restricted to ITP patients refractory to splenectomy or to those in whom surgery is contraindicated in many countries [8]. In addition, while the efficacy of and tolerance to TPO-RA is elucidated, its long-term toxicity is still not known [9].

The immunosuppressive drugs azathioprine, danazol, cyclosporine A, dapsone, mycophenolate mofetil, cyclophosphamide, vincristine, and vinblastine are all considerably variable with respect to the response achieved in individual patients when used as a second-line treatment; however, none of these therapies have been compared in randomized trials [10]. Dapsone was first described as a po-

tential therapeutic agent for ITP in 1988 when it improved the platelet count in a patient with systemic lupus erythematosus [11]. Since then, several retrospective studies have reported the efficacy of dapsone in ITP, with a response rate of 29–63% and a platelet count of $>50\times10^9$/L [12-15]. Herein, we report the results of the use of dapsone in 9 patients with chronic ITP.

MATERIALS AND METHODS

This retrospective analysis of the data for ITP patients treated with dapsone was conducted between May 2013 and January 2016 at Seoul National University Bundang Hospital and Dongtan Sacred Heart Hospital. The diagnosis of ITP was based on the recommendations of the 2009 international working group [16]. Data collection was approved by the Institutional Review Boards of both hospitals.

Nine patients with ITP received dapsone orally at a dose ranging from 50 to 100 mg/day (5 started at 100 mg/day, and 4 started at 50 mg/day titrated up to 100 mg/day as tolerated). No other drugs active in ITP were used concurrently with the dapsone. All patients had normal levels of glucose-6-phosphate dehydrogenase. The response criteria were defined on the basis of the published consensus guidelines [16]. Complete response (CR) was defined as a platelet count of $\geq100\times10^9$/L and the absence of bleeding, and response (R) was defined as a platelet count of $\geq30\times10^9$/L and at least a 2-fold increase over the baseline count and absence of bleeding. Platelet counts were confirmed on at least 2 occasions, at least 7 days apart when used to define CR and R, or 1 day apart when used to define no response (NR) or loss of response.

RESULTS

There were 3 male and 6 female patients with a median age at the onset of treatment with dapsone of 63 years (range, 43–73 yrs). The median duration of ITP before dapsone treatment was 57.9 months (range, 5.5–254.8 mo). All the patients received corticosteroids as the first-line treatment. Three of the patients had previously undergone splenectomy; 1 patient (#7) was not eligible for surgery due to old age, and the remaining patients refused the surgery. All patients had received at least 4 other immunosuppressive drugs before the initiation of dapsone therapy (median, 7 agents, range, 4–8), and their median platelet count before dapsone therapy was 4×10^9/L (range, $3–27\times10^9$/L). These patient details are summarized in Table 1.

Only 1 patient (#2) responded to dapsone therapy, with a time to response of 2.7 months and response duration of 7.3 months (Fig. 1A). This young female patient had no history of splenectomy and had been previously treated with 5 immunosuppressive agents; however, she discontinued dapsone therapy after 18.6 months owing to loss of response. One patient (#3) remained on dapsone therapy for 39.3 months and achieved a platelet count of $>30\times10^9$/L, which was less than twice that of the initial count, and there were no bleeding episodes (Fig. 1B). The remaining 7 patients discontinued dapsone therapy, and 3 of these 7 patients had been treated with dapsone for fewer than 30 consecutive days. Six patients had switched treatment because of a lack of response to dapsone, and 1 patient (#8) required with-

Table 1. Patient data and results of dapsone treatment for immune thrombocytopenia.

	Patient								
	1	2	3	4	5	6	7	8	9
Age (yrs)/gender	46/M	46/F	66/M	58/F	69/F	63/M	70/F	73/F	43/F
Time from diagnosis to dapsone, mo	5.5	254.8	31.4	57.9	218.5	12	5.5	108.1	134.0
Previous treatment									
Corticosteroids	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immunoglobulin	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Splenectomy	No	No	No	No	Yes	No	No	Yes	Yes
Danazol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Azathioprine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Cyclosporine A	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Cyclophosphamide	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No
Vincristine	No	No	Yes	No	Yes	Yes	No	Yes	No
Rituximab	No	No	No	No	No	No	Yes	No	No
TPO-RA	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
Platelet count before dapsone, $\times10^9$/L	3	3	27	10	3	4	3	6	6
Treatment duration, mo	3.7	18.6	39.3[a]	0.8	0.4	1.4	1.4	0.7	1.7
Response[b]	No	Yes	No	No	No	No	No	No	No

[a]Patient remained on dapsone for 39.3 months. [b]Response defined as platelet count $\geq30\times10^9$/L and at least 2-fold increase over the baseline count and absence of bleeding.
Abbreviations: F, female; M, male; TPO-RA,thrombopoietin-receptor agonist.

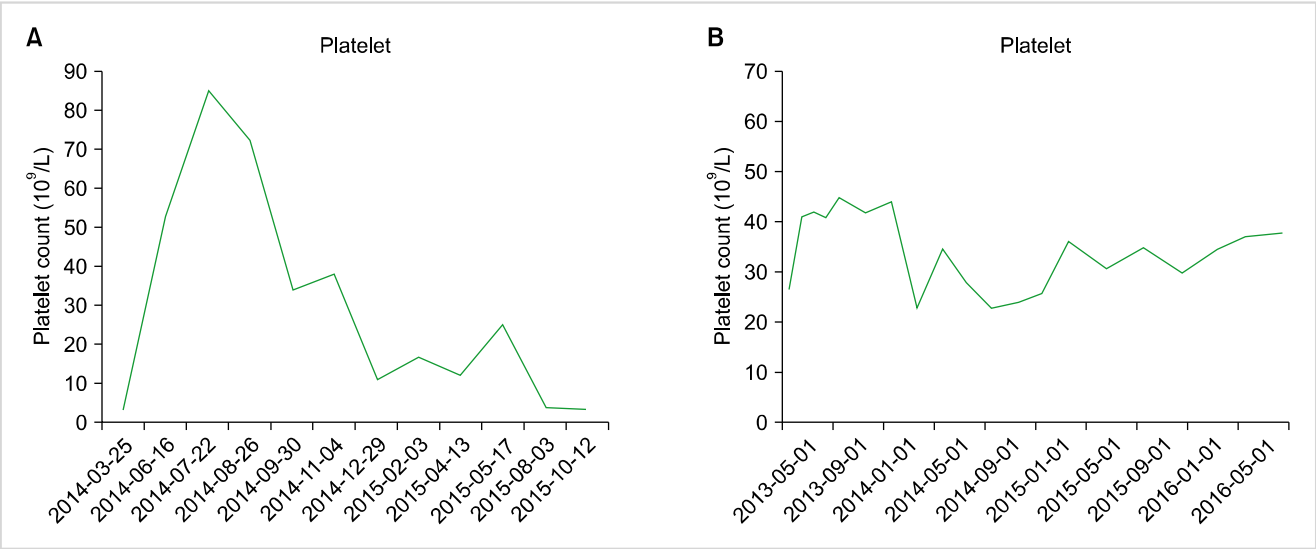

Fig. 1. Platelet count during dapsone treatment of **(A)** patient 2 and **(B)** patient 3.

drawal from treatment because of dapsone hypersensitivity syndrome (DHS). The 73-year-old woman presented with skin rash on her face and neck 2 weeks after dapsone initiation (100 mg/day). The skin rash was associated with high fever, eosinophilia, hepatitis, and multiple lymphadenopathies above and below the diaphragm (Fig. 2). Dapsone was discontinued and prednisolone was given at 1 mg/kg, and her clinical symptoms gradually improved. After 3 months from the initiation of steroid therapy, she experienced exacerbation of her hepatitis when an attempt was made to reduce the steroid dose. Methylprednisolone at a dose of 1 mg/kg was given for 10 days, and the prednisolone was tapered off over the next 7 months with complete normalization of liver function and resolution of the lymphadenopathy.

The median pre-treatment hemoglobin level of all patients was 11.8 g/dL and the median nadir of on-treatment hemoglobin was 10.5 g/dL which was not a significant decrease (P=0.095). None of the patients showed significant development of hemolysis.

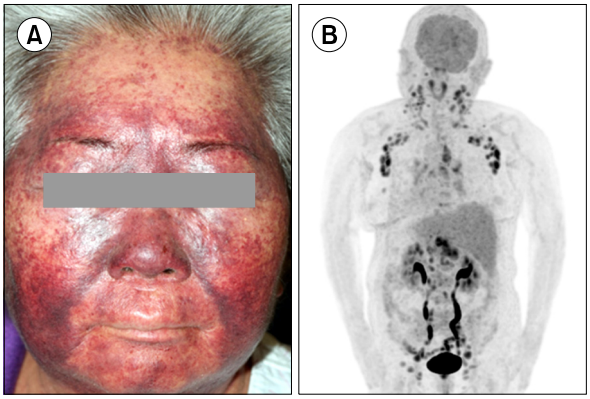

Fig. 2. Clinical feature of a patient with dapsone hypersensitivity syndrome. **(A)** Skin erythema with extensive scaling on face and neck. **(B)** Multiple hypermetabolic lymph nodes in both neck and axilla, portocaval, celiac axis, retrocrural, both paraaortic, aortocaval, and both external iliac and inguinal areas.

DISCUSSION

The goals of ITP treatment are to maintain the platelet count to avoid the risk of serious bleeding and to limit drug toxicity [17]. Several retrospective studies demonstrated that dapsone provides an effective, inexpensive, and well-tolerated alternative for patients with refractory ITP (Table 2) [12-15, 18-20].

The mechanism of action of dapsone in ITP is unknown. A possible mechanism is that dapsone-induced hemolysis leads to erythrophagocytosis by the reticuloendothelial system, preventing sequestration and destruction of platelets [21]. An alternative hypothesis is that dapsone is an immunomodulatory drug [21]. Furthermore, there are concerns regarding both the efficacy of dapsone and the lack of information about any factors that predict the response to treatment. Godeau *et al.* [13] showed a larger decrease in hemoglobin values in responders than in nonresponders and a trend toward fewer responses in the patients who had undergone splenectomy. Conflicting results, however, have been reported in other studies, where the increase in platelet count did not correlate with the decrease in hemoglobin level [12, 15]. Godeau *et al.* (1993) [14] showed that platelet counts before initiation of dapsone therapy were significantly higher in the responders than in the nonresponders. However, Vancine-Califani *et al.* [19] showed that pretreatment characteristics were not correlated with the response to dapsone.

In current study, the 11.1% response rate was worse than that in previous studies. This low response rate can be ex-

Table 2. A summary of studies on dapsone therapy in patients with ITP.

	Durand *et al.*	Godeau *et al.*	Hernández *et al.*	Godeau *et al.*	Damodar *et al.*	Vancine-*et al.*	Zaja *et al.*
Country	France	France	Spain	France	India	Brazil	Italy
N of patients	5	21	15	66	90	52[a]	20[b]
Median age, yrs (range)	76 (68–87)	37 (22–79)	58 (16–84)	43 (26–68)	21 (3–61)	38 (13–78)	51 (27–74)
Time from diagnosis to dapsone, mo	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)
N of prior treatments, median (range)	2 (0–4)	2 (1–9)	1 (1–2)	3(0–10)	NA	NA	NA
Platelet count before dapsone, $\times 10^9$/L (range)	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)
Dose of dapsone, day	75 mg	100 mg	100 mg	100 mg	1–2 mg/kg	100 mg	100 mg
Median treatment duration, mo (range)	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)
Response rate[c], %	100	29	40	50	63	44	55
Status of combination therapy	No	Yes	No	Yes	No	No	No

[a]Forty patients were found to have primary ITP. [b]Sixteen patients were found to have primary ITP. [c]Response to dapsone was defined as a platelet count $>50\times10^9$/L.
Abbreviations: CR, complete response ($>10\times10^9$/L); ITP, immune thrombocytopenia; NR, no response ($<5\times10^9$/L); PR, partial response ($5–10\times10^9$/L); R, response ($>5\times10^9$/L).

plained by the disease status before dapsone therapy. The patients in this study had been more heavily treated with other immunosuppressive agents and demonstrated profound thrombocytopenia. Oo and Hill [22] also investigated the role of dapsone in patients who relapsed or were refractory to multiple lines of therapy and showed a low overall response rate of 27%, and only a 9% response at 6 months.

Assessment of both tolerance and adverse events in ITP patients on dapsone therapy is crucial, and although the most frequent adverse effect of dapsone is hemolytic anemia, a dose reduction in most cases resolves as a mild hemolysis [23]. The patients in this study had a tendency toward a decreased pre-therapy hemoglobin level compared with post-therapy levels; however, the difference was not statistically significant. Sauvetre *et al.* [24] reported that 7.3% of patients had cutaneous reactions to dapsone and that only 2.6% had severe reactions, such as DHS. In the current study, 1 patient who presented with a high-grade fever, rash, and multi-organ involvement was managed successfully with systemic steroids.

The limitations of this study were inherent in its retrospective nature and the small number of patients from only 2 centers. Nevertheless, this detailed review can guide physicians who may consider dapsone in the treatment of chronic ITP. In conclusion, although dapsone can be a cost-effective option in patients with chronic ITP, it might be less effective in heavily pretreated patients with profound thrombocytopenia.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood 2009;113:6511-21.
2. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood 2004;103:1364-9.
3. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood 2001;97:2549-54.
4. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood 2008;112:999-1004.
5. Michel M, Suzan F, Adoue D, et al. Management of immune thrombocytopenia in adults: a population-based analysis of the French hospital discharge database from 2009 to 2012. Br J Haematol 2015;170:218-22.
6. Rodeghiero F, Ruggeri M. Is splenectomy still the gold standard for the treatment of chronic ITP? Am J Hematol 2008;83:91.
7. Neunert CE. Current management of immune thrombocytopenia. Hematology Am Soc Hematol Educ Program 2013;2013:276-82.
8. Ghanima W, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood 2012;120:960-9.
9. Cuker A, Cines DB, Neunert CE. Controversies in the treatment of immune thrombocytopenia. Curr Opin Hematol 2016;23:479-85.
10. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune

thrombocytopenia. Blood 2010;115:168-86.
11. Moss C, Hamilton PJ. Thrombocytopenia in systemic lupus erythematosus responsive to dapsone. BMJ 1988;297:266.
12. Damodar S, Viswabandya A, George B, Mathews V, Chandy M, Srivastava A. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults-a report on 90 patients. Eur J Haematol 2005;75:328-31.
13. Godeau B, Durand JM, Roudot-Thoraval F, et al. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. Br J Haematol 1997;97:336-9.
14. Godeau B, Oksenhendler E, Bierling P. Dapsone for autoimmune thrombocytopenic purpura. Am J Hematol 1993;44:70-2.
15. Hernández F, Linares M, Colomina P, et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 1995;90:473-5.
16. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
17. Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. Blood 2016;128:1547-54.
18. Durand JM, Lefèvre P, Hovette P, Mongin M, Soubeyrand J. Dapsone for idiopathic autoimmune thrombocytopenic purpura in elderly patients. Br J Haematol 1991;78:459-60.
19. Vancine-Califani SM, De Paula EV, Ozelo MC, Orsi FL, Fabri DR, Annichino-Bizzacchi JM. Efficacy and safety of dapsone as a second-line treatment in non-splenectomized adults with immune thrombocytopenic purpura. Platelets 2008;19:489-95.
20. Zaja F, Marin L, Chiozzotto M, Puglisi S, Volpetti S, Fanin R. Dapsone salvage therapy for adult patients with immune thrombocytopenia relapsed or refractory to steroid and rituximab. Am J Hematol 2012;87:321-3.
21. Hill QA. How does dapsone work in immune thrombocytopenia? Implications for dosing. Blood 2015;125:3666-8.
22. Oo T, Hill QA. Disappointing response to dapsone as second line therapy for primary ITP: a case series. Ann Hematol 2015;94:1053-4.
23. Rodrigo C, Gooneratne L. Dapsone for primary immune thrombocytopenia in adults and children: an evidence-based review. J Thromb Haemost 2013;11:1946-53.
24. Sauvetre G, MahÈvas M, Limal N, et al. Cutaneous rash and dapsone-induced hypersensitivity syndrome a common manifestation in adult immune thrombocytopenia. Presentation and outcome in 16 cases. Am J Hematol 2015;90:E201-2.