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Fast platelet recovery is associated with remission in primary immune thrombocytopenia

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ABSTRACT

Objectives: We aimed to reveal predictors of response and response duration to steroid therapy in first line of treatment in immune thrombocytopenia (ITP).

Methods: Fifty patients, who were diagnosed with ITP in hematology department of Suleyman Demirel University Hospital between 2005-2019, who had sufficient clinical and laboratory data, followed up for at least one year and received corticosteroid treatment in first line, were evaluated retrospectively for treatment response time, remission, prognosis on their first line treatment. The patients who maintained remission for more than 12 months was defined as group 1 and those who did not achieve remission or relapsed in less than 12 months were defined as group 2.

Results: Twenty-two (44%) patients responded in first 3 days of the treatment, 16 (32%) patients in 4 to 7 days and 4 (8%) patients responded in more than 7 days. Eighty-four percent (n = 42) of these patients had complete response to corticosteroid treatment. When the remission maintenances were examined, it was observed that 22 (44%) patients were in remission for more than 12 months, 20 (40%) patients were in remission with treatment but relapsed before 12 months and 8 (16%) patients did not respond to corticosteroid treatment. When the response time to treatment in patients with or without remission was compared, remission was significantly lower in those who responded late to treatment (p = 0.01). When the response rates to corticosteroid treatment of patients in group 1 and 2 were evaluated, it was found that the response time to treatment was not related to the maintenance of remission (p = 0.267).

Conclusions: Faster response time to treatment produced higher remission rates but, we could not find any relationship between response time to treatment and duration of remission.

Keywords: Immune thrombocytopenia, remission, fast recovery, prognosis

Primary immune thrombocytopenia (ITP) is a disease that was associated with the immune-mediated destruction of platelets. ITP is divided into three stages: newly diagnosed (covering 3 months after diagnosis), persistent (covering between 3 and 12 months after diagnosis), chronic (disease lasting more than 12 months) [1, 2]. Apart from the immune-mediated destruction caused by autoantibodies against gly-

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coprotein (GP) IIb-IIIa and Gp Ib-IX complex, decreased platelet production, which cannot keep up with this increased destruction, is thought to play a role in the pathogenesis of ITP [3-5]. Some polymorphisms in major tissue compatibility complexes (MHC), chemokines, proinflammatory cytokines, anti-inflammatory cytokines and their receptors have been observed in patients with ITP [6]. There is no specific test used to diagnose ITP. In most cases, primary ITP is a diagnosis of exclusion made by a careful history, physical examination, complete blood count, and peripheral smear examination [7, 8].

Treatment decision in adult ITP should be made according to the patient's current bleeding severity, bleeding risk, activity level, treatment side effects, and patient preference [9]. Corticosteroid therapy is preferred unless there is a contraindication to its use in the first step in treatment [1, 9, 10]. Intravenous immunoglobulin (IVIG), splenectomy, immunosuppressive agents, rituximab, thrombopoietin receptor agonists are other options in the treatment of ITP [9]. Corticosteroid therapy in first line leads to 85-9 % of responses but relapses are common [11]. There are few studies evaluating the predictors of response to corticosteroid treatment so this study aimed to reveal predictors of response and response duration to steroid therapy in first line of treatment in ITP.

METHODS

Fifty patients, above 18 years old and who were diagnosed with ITP in the hematology department of Suleyman Demirel University Hospital between 2005-2019, who had sufficient clinical and laboratory data, followed up for at least one year and received corticosteroid treatment in first line, were evaluated retrospectively. Patients who were pregnant, who had a diagnosis that can be attributed to isolated thrombocytopenia (drug induced thrombocytopenia, connective tissue disease, disseminated intravascular coagulation) were excluded from the study. Patients who were diagnosed with malignancy were also excluded from the study. The study was approved by ethics committee of Suleyman Demirel University Medical Faculty Clinical Research Ethics Committee on 05.04.2019 with protocol number 134 and detailed informed consent was obtained from all patients. The clinical and laboratory data, treatment responses and time to achieve the response were examined. Response and relapse were defined according to the immune thrombocytopenia guide of American Society of Hematology [12]. Age and gender at admission, presence of symptoms related to bleeding, presence of additional disease, presence of drugs that can affect bleeding, especially fever, hepatomegaly, splenomegaly, lymphadenopathy in physical examinations, presence of thrombocyte transfusion, laboratory tests; total blood count parameters, hepatitis serology, C-reactive protein (CRP) level, presence of antinuclear antibody (ANA) and positivity degree, reticulin fiber grade of patients who underwent bone marrow biopsy, response of patients to corticosteroid treatment (response was defined as platelet count above 30,000/mm^3), time to response, presence of remission (remission was determined as platelet count above 100,000/mm^3), ability to maintain remission for one year or longer were recorded retrospectively from medical health records. The patients who maintained remission for more than 12 months was defined as group 1 and those who did not achieve remission or relapsed in less than 12 months were defined as group 2 and these two groups were compared for response rate, response time to treatment and maintenance of response. All patients received 1 mg/kg/day methylprednisolone for twenty-one days and then slowly tapered and stopped for up to 3 months.

Statistical Analysis

IBM SPSS Statistics 21.00 statistical program was used for statistical calculations. The conformity of the quantitative data to the normal distribution was examined with the Kolmogorov Smirnov test. Student's t test and One Way Anova were used in independent groups for statistical comparisons for variables with normal distribution. Descriptive statistics were presented as standard deviation. Mann-Whitney U and Kruskall Walls tests were used for statistical comparisons for variables that were not normally distributed. Descriptive statistics were shown as mean ± standard deviation. Chi-square analysis was used for statistical comparisons for categorical variables and descriptive statistics were shown as frequency (%). $P < 0.05$ was considered statistically significant.

RESULTS

Of the 50 patients, 35 (70%) were female and 15 (30%) were male. The mean age of the patients was 49.4 ± 17. 1 years, women's mean age was 48.4 ± 17.1 years, and men's mean age was 51.7 ± 17.3 years. When all genders were compared, no statistically significant difference was found between their ages and in terms of response to corticosteroid treatment and remissions ($p > 0.05$).

At diagnosis, 92% (n = 46) of the patients had symptoms associated with ITP. Only 8% (n = 4) of the patients were asymptomatic and were diagnosed during their routine examinations. In 84.8% of symptomatic patients, the presenting symptom was mucocutaneous bleeding. For additional physical findings, hepatomegaly due to grade 3 hepatosteatosis was found in one patient, hepatosplenomegaly was found in one patient. Fever and lymphadenopathy were not detected in any patient at admission.

No additional disease was detected in 31 patients, and additional diseases that would not affect the coagulation cascade were detected in 19 patients. When the drug use of the patients was examined, 36 patients did not use any drugs, 6 patients used anticoagulant-antiaggregant drugs as additional drugs, and 8 patients used other drugs that did not affect coagulation. When the relationship between the presence of additional disease and remission was examined, no significant difference was found between the groups ($p = 0.413$). Similarly, when the additional drug use of the patients and their remission were compared, no significant difference was found between the groups ($p = 0.441$).

When the laboratory parameters of the patients were examined, the mean white blood cell (WBC) count of the group 1 was 6.88 ± 1.78 ×103/µL, while the mean WBC of group 2 was 7.93 ± 2.73 ×103/µL and, no significant difference was observed between the groups ($p = 0.257$). Also, no significant difference was found between mean leukocyte subgroups and remission groups ($p = 0.544$, $p = 0.624$ and $p = 0.567$, respectively). The mean hemoglobin was 12.9 ± 2.1 g/dL, and no statistically significant difference was found between mean haemoglobin and remission groups ($p = 0.512$, T test). Likewise, there was no significant difference between mean of MCV and hematocrit and remission groups ($p = 0.677$ and $p = 0.580$, T test; respectively). Mean platelet value was 10.4 ± 8.2 × 103/µL, the mean MPV value was 9.4 ± 1.4 fL and no statistically significant difference was observed

Table 1. Comparison of laboratory parameters of patients who maintained remission for more than 12 months and other patients

Laboratory Parameters	Group with remission lasting more than 12 months (n = 24)	Group with no remission and relapse in less than 12 months (n = 34)	Overall average	*p* value
WBC (× 10^3/µL)	6.88 ± 1.78	7.93 ± 2.73	7.45 ± 2.37	0.257
NEU*(× 10^3/µL)	7.13 ± 2.84	5.14 ± 0.45	5.84 ± 7.81	0.544
LYM (× 10^3/µL)	1.82 ± 0.45	1.99 ± 1.02	1.29 ± 0.79	0.624
MON*(× 10^3/µL)	0.60 ± 0.22	0.95 ± 0.39	0.75 ± 1.41	0.567
HGB (g/dL)	12.4 ± 2.2	13.3 ± 1.9	12.9 ± 2.1	0.512
MCV (fL)	83.5 ± 10.4	84.8 ± 4.9	84.4 ± 7.4	0.677
HCT (%)	36.7 ± 5.3	38.9 ± 5.3	38.1 ± 5.8	0.580
PLT*(× 10^3/µL)	9.1 ± 6.5	10.8 ± 8.4	10.4 ± 8.2	0.260
MPV (fL)	9.1 ± 1.6	9.5 ± 1.3	9.4 ± 1.4	0.765
CRP*(mg/L)	7.9 ± 6.4	20.6 ± 9.2	14.9 ± 3.4	0.212

Parameters with * do not comply with the regular distribution and were compared with the Mann- Whitney U test, and other parameters were compared with the t test. WBC = White Blood Count, NEU = Neutrophil, LYM = Lymphocyte, MON = Monocyte, HGB = Hemoglobin, MCV = Mean Corpuscular Volume, HCT = Hematocrit, PLT = Platelet, MPV = Mean Platelet Volume, CRP = C-reactive Protein

Table 2. Comparison of laboratory parameters of patients who went into remission and maintained for more than 12 months and relapsed before 12 months

Laboratory Parameters	Patients in remission			
	Maintenance longer than 12 months (n = 24)	Relapse before 12 months (n = 25)	Overall average (n = 49)	*p* value
WBC (× 10^3/µL)	6.88 ± 1.78	7.79 ± 2.03	7.40 ± 1.98	0.131
NEU*(× 10^3/µL)	7.12 ± 2.84	4.74 ±1.68	5.86 ± 8.42	0.668
LYM (× 10^3/µL)	1.83 ± 0.46	2.22 ± 0.82	2.01 ± 0.7	0.167
MON*(× 10^3/µL)	0.61 ± 0.21	1.12 ± 2.34	0.81 ± 1.53	0.889
HGB (g/dL)	12.4 ± 2.2	13.2 ± 2.1	12.9 ±2.2	0.618
MCV (fL)	83.5 ± 10.4	84.3 ± 4.3	84.0 ± 7.6	0.875
HCT (%)	36.7 ± 5.3	38.6 ± 5.8	38.0 ± 6.0	0.632
PLT*(× 10^3/µL)	9.1 ± 6.5	10.6 ± 8.8	10.3 ± 8.4	0.283
MPV (fL)	9.1 ±1.6	9.5 ± 1.3	9.3 ± 1.5	0.236
CRP*(mg/L)	7.9 ± 6.4	26.4 ± 12.6	16.6 ± 37.9	0.490

Parameters with * do not comply with the regular distribution and were compared with the Mann- Whitney U test, and other parameters were compared with the t test. WBC = White Blood Count, NEU = Neutrophil, LYM = Lymphocyte, MON = Monocyte, HGB = Hemoglobin, MCV = Mean Corpuscular Volume, HCT = Hematocrit, PLT = Platelet, MPV = Mean Platelet Volume, CRP = C-reactive Protein

in the comparison of both parameters between the remission groups ($p = 0.260$, Mann Whitney U and $p = 0.765$, T test; respectively). There was no significant difference in the comparison between mean CRP and remission groups ($p = 0.212$) (Table 1). When the laboratory parameters of remission groups were evaluated, no significant difference was observed in any of the parameters (Table 2).

When viral markers were examined, except for one patient whose data were missing, all patients were Anti-HIV, Anti HCV and HbsAg negative 39 patients were Anti-HBs Negative and 10 patients were positive. Eleven patients were Anti-Nuclear Antibody (ANA) positive (7 of them +; 4 of them ++). Thirty-nine patients were ANA negative. When two remission groups were evaluated for ANA positivity, there was no statistically significant difference between the remission groups (Table 3).

Bone marrow aspiration biopsy was performed in 28 patients and, 8 patients had grade 0; 8 patients grade 1; 9 patients grade 2 and 3 patients had grade 3 reticulin fiber. Reticulin fiber grade 1 and 2 was higher

Table 3. ANA status

Laboratory status	Group with remission lasting more than 12 months (n = 20)	Group with no remission and relapse in less than 12 months (n = 30)	*p* value
ANA positive	7	4	0.159
+	4	3	
++	3	1	
+++	0	0	
++++	0	0	
ANA negative	13	26	

ANA = Anti-nuclear antibody

in group 2 patients compared to group 1 however; no significant difference was found between groups (Table 4).

Thirty-four percent of the patients received platelet transfusion during treatment period. Of the patients who received platelet transfusion, 10 remained in remission for more than 12 months, and 7 either never entered remission or relapsed before 12 months of remission. Platelet transfusions did not have a statistically significant effect on remission of the patients ($p = 0.543$).

Twenty-two (44%) patients responded in first 3 days of the treatment (PLT > 30,000) and 16 (32%) patients in 4 to 7 days. It was observed that 4 (8%) patients responded in more than 7 days. 84% (n=42) of these patients had complete response (PLT > 100,000) to corticosteroid treatment. When the remission maintenances were examined, it was observed that 22 (44%) patients were in remission for more than 12 months (PLT > 100,000), 20 (40%) patients were in remission with treatment but relapsed before 12 months (PLT < 100,000) and 8 (16%) patients did not respond to corticosteroid treatment. When the response time to treatment in patients with or without remission was compared, remission was significantly lower in those who responded late to treatment ($p = 0.01$). When the response rates to corticosteroid treatment of patients in group 1 and 2 were evaluated, it was found that the response time to treatment was not related to the maintenance of remission ($p = 0.267$) (Table 5).

DISCUSSION

ITP is a chronic disease in adults, while 80-90 % of patients respond to primary treatment; most patients relapse and need additional treatment [11]. Corticosteroids are the main backbone of first line treatment; prednisolone, methylprednisolone and high dose dexamethasone was used effectively for treatment. High dose dexamethasone seemed to induce faster response and less long-term toxicity compared to prednisone [13], but overall prognosis of the disease did not significantly change in either of treatment and, at 12 months response rates were similar [14]. According to ASH guidelines for immune thrombocytopenia, both can be used as a primary treatment [12]. In another study, response was observed in 63.6% (n = 49) of the patients who were given corticosteroid treatment, and 28.6% (n = 14) of these patients relapsed over time [15]. In a study examining 43 ITP patients over 60 years of age, the responses of the patients to corticosteroid treatment at the 1st and 6th months were examined, and the response rate at 1 and 6 month was found to be 61% and 33% respectively [16]. In a study with 137 patients receiving steroid therapy, complete response and relapse were observed in 51.9% and 58.2 % of the patients during 33-month follow-up [17]. Stasi *et al*. [18] found that with prednisone treatment complete response was observed in 38.8% of these patients and only 18.7% of these patients, maintained their response at 6-month follow-up. Leung *et al*. [19] showed that, in 142 patients, complete response was

Table 5. Comparison of response rate to corticosteroid therapy and maintenance of remission

		Remission > 12 months	Relapse	Total	*p* value
Response to steroid	3 days	9	13	22	
	4-7 days	10	6	16	0.267
	More than 7 days	3	1	4	
Total		22	20	42	
		Remission (for any period of time)	Never in remission	Total	
Response to steroid	3 days	22	1	23	**0.010**
	4-7 days	16	3	19	
	More than 7 days	4	4	8	
Total		42	8	50	

47.2% and 46% of these patients maintained their response at 470-month follow-up. Chang *et al*. [11] found that, 63 % of patients with frontline steroid therapy were relapsed at median of 9.5 months. We found that, 44% of patients maintained remission for more than 12 months, compatible with literature. Response rates to corticosteroid therapy and the duration of these responses have been reported at different rates in literature. The differences for the rate of complete response to steroid treatment in the literature might be due to the distinct follow-up period, inclusion criteria, and response definitions of different studies.

Response time to treatment could be an attractive prognostic indicator in ITP, but evidence was lacking. In one study, high dose dexamethasone produced faster platelet response than prednisone (3 to 5 days respectively) but in twelve months follow-up, complete response rates were comparable (32.1 % for high dose dexamethasone and 34.1 % for prednisone) [13]. We also found that faster response time did not produce longer remissions, but faster response time produced significantly higher remission rates, and this was compatible with the literature.

Limitations

Retrospective design was the main limitation for our study. Our study evaluated 50 patients; a prospective study with more patients might show much significant results. Besides, we could not find another study directly addressing the response time to treatment and remission issue; this was the main strength of the study. It would be valuable to assess the hypotheses in a prospective study.

CONCLUSION

We showed that faster response time to treatment produced higher remission rates but, we could not find any relationship between response time to treatment and duration of remission. Prospective studies with large number of patients are needed to evaluate the issue.

Authors' Contribution

Study Conception: FGH, DÖ; Study Design: DÖ; Supervision: FGH, DÖ, EGA; Funding: N/A; Materials: FGH; Data Collection and/or Processing: FGH, AYH; Statistical Analysis and/or Data Interpretation: AYH; Literature Review: FGH, DÖ; Manuscript Preparation: FGH, DÖ, EGA and Critical Review: FGH, DÖ, EGA, AYH.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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