Original Article

An Observational Study To Assess The Treatment Response In Adult Patients With Chronic Itp

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Abstract

BACKGROUND AND OBJECTIVES: We have studied the clinical profile of adult patients with chronic immune thrombocytopenia (ITP) and treatment response to different therapies, focusing mainly on second-line therapy.
METHODOLOGY: 42 patients with chronic ITP were included in the study over 2 years (1st April 2020 to 31st March 2022) from Chettinad Hospital And Research Institute, Kelambakkam, Tamilnadu. Patients were interviewed for detailed history, including active complaints, past medical information, current therapy, and blood counts. A complete clinical examination included documentation of bleeding areas and examination of other systems to rule out underlying problems. These patients were further followed, and responses to the respective treatments were noted.
RESULTS: Out of 42 patients included in the study, most patients (40.5%) were <30 years old, whereas 88.1% were female and 11.9% were male. In the case of comorbidity, we have seen that most patients (88.1%) do not have any comorbid condition. In comparison, 2.4%, 4.8%, 4.8%, and 2.4% of patients have DM, HTN, or thyroid disorders, and 2.4% of patients have other comorbid conditions, respectively. Further, 42.9%, 31.0%, 16.7%, 16.7%, and 2.4% of patients presented with menorrhagia symptoms, mucosal symptoms, asymptomatic condition, skin symptoms, and ich, respectively. However, 52.4%, 38.1%, and 9.5% of patients had platelet count <10000, 10000-30000, and >30000 at presentation, respectively. There was a significant difference between the third and fourth therapy response. The duration of therapy response with and without treatment showed that azathioprine and dapsone response was similar to other standard second-line therapies.
CONCLUSION: Our study shows a response of azathioprine and dapsone similar to other standard second-line therapies.

Keywords: Chronic ITP, Immune thrombocytopenia, Steroids, Azathioprine, Dapsone, Splenectomy, Rituximab, Thrombopoietin receptor agonists.

INTRODUCTION:

Immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenic purpura, is an immune-mediated acquired disease of adults and children. It is characterized by a transient or persistent decrease of the platelet count and, depending upon the degree of thrombocytopenia, an increased risk of bleeding[1,2,3]. The prevalence of ITP was higher in adults than in children (12.1 vs 8.1 per 100,000 patients)[4]. In general, ITP in adults is more prevalent in women (30–60 years)[5].

First-line treatments for ITP include corticosteroids (prednisone, dexamethasone), intravenous immunoglobulin (IVIg), and anti-D (Rh0) immunoglobulin. While corticosteroids and immunoglobulins produce an initial response in most patients (60%-70% and 90%, respectively), the response is usually transient (<6 months and 2–4 weeks, respectively), and the medications must be readministered if the patient's platelet count does not stabilize Repeated or prolonged administration of first-line therapies is typically not suitable due to significant adverse effects with

corticosteroids and high cost, inconvenience of frequent infusions, and debilitating post-infusion headache with immunoglobulins[6-10].

Splenectomy, thrombopoietin receptor agonists (TPO-RAs), and rituximab are current second-line treatment options. Other agents, including mycophenolate mofetil, azathioprine, danazol, dapsone, vinca alkaloids, sirolimus, cyclosporine, and cyclophosphamide have been used in ITP as alternative treatments since they are less expensive compared with rituximab and the TPO-RAs. These agents may play an important role in the second-line treatment of ITP in countries where access to standard second-line therapies is limited[2,6,8].

In developing countries, many people are not affordable to receive standard second-line treatment, and splenectomy is an invasive procedure that refrained patients. So, alternatives like azathioprine, danazol, dapsone, mycophenolate mofetil, etc., are used as second-line therapy. Therefore, the present study aimed to observe the treatment response in patients diagnosed with chronic ITP, focusing on alternative second-line agents.

MATERIALS AND METHODS

The present study was observational in which adult patients with chronic ITP (ITP lasting more than 12 months since initial diagnosis) qualified the inclusion and exclusion criteria and were in follow-up at Meenakshi Mission Hospital, Madurai, from April 2020 to March 2021 were included in the study. Before initiating the study, the ethical committee approval and written informed consent were obtained from patients.

Inclusion criteria: All the patients above the age of 18 years who got diagnosed with chronic immune thrombocytopenia (ITP >12 months from initial diagnosis).

Exclusion criteria: Patients diagnosed with immune thrombocytopenia (ITP) recently <12 months. · Patients diagnosed with other causes of thrombocytopenia like SLE, APLA, CLD, CKD, HIV, HCV, drug-induced thrombocytopenia, and Lymphoproliferative disorders.

Patients were interviewed during their follow-up, and detailed history, including active complaints, past medical information (regarding the clinical details at diagnosis, other comorbidities, Initial treatment, relapses, splenectomy, and follow-up), current therapy, and blood counts were obtained, or review of their hospital records (laboratory reports/ physician documentation in hospital charts/hospital discharge summaries). A complete clinical examination included documentation of bleeding areas and examination of other systems to rule out underlying problems. In addition, an examination of the abdomen was done to identify splenomegaly. These patients were further followed, and response to the respective treatments was noted. Details regarding active complaints, blood counts, current therapy, and its response were recorded at each follow-up.

Response criteria:

The definition of response criteria was as follows:

- **Complete response (CR):** Platelet count ≥ 100 x109 /L and absence of bleeding.
- **Response (R):** Platelet count ≥ 30 x109 /L and absence of bleeding.
- **No-Response (NR):** Platelet count < 30 x109 /L or bleeding.
- **Duration of response:** Measured from the achievement of CR or R to the loss of CR or R.

Statistical analysis

Data analysis was done by using SPSS 20 and Minitab 16. In descriptive statistics, the continuous variable will be expressed as Mean and Standard deviation. Categorical variables will be expressed as frequency and percentage. The Chi-square test and fisher's exact test will determine the association between the categorical variables. $P < 0.05$ will be considered statistically significant.

RESULTS:

Clinical characteristics: Out of 42 patients included in the study, most patients (40.5%) were <30 years old, whereas 88.1% were female and 11.9% were male. In the case of comorbidity, we have seen that most patients

(88.1%) do not have any comorbid condition. In comparison, 2.4% of patients have DM, 4.8% have HTN, 4.8% have thyroid disorders, and 2.4% have other comorbid conditions.

Further, 42.9% of patients presented with menorrhagia symptoms, 31.0% of patients presented with mucosal symptoms, 16.7% were asymptomatic, 16.7% presented skin symptoms, and 2.4% of patients presented with ich. However, 52.4%, 38.1%, and 9.5% of patients had platelet count <10000, 10000-30000, and >30000 at presentation, respectively (Table 1).

Table 1: Clinical characteristics of patients

		Frequency (n=42)	Percentage
AGE GROUP	<30	17	40.5%
	31-40	9	21.4%
	41-50	10	23.8%
	51-60	4	9.5%
	>61	2	4.8%
SEX	FEMALE	37	88.1%
	MALE	5	11.9%
COMORBIDITIES	DM	1	2.4%
	HTN	2	4.8%
	THYROID DISORDERS	2	4.8%
	OTHERS	1	2.4%
	NIL	37	88.1%
SYMPTOMS AT PRESENTATION	ASYMPTOMATIC	7	16.7%
	ICH	1	2.4%
	MENORRHAGIA	18	42.9%
	MUCOSAL	13	31.0%
	SKIN	7	16.7%
PLATELET COUNT AT PRESENTATION	<10000	22	52.4%
	10000-30000	16	38.1%
	>30000	4	9.5%

Treatment and response of chronic ITP:

During the first therapy, for complete response, 55% complete response was observed for steroid, and 50% response was observed for IVIG.

During the second therapy, for complete response, 50%, 30%, complete response was observed for azathioprine and dapsone, respectively. During the second therapy, in partial response, 27.3%, 40%, 60%, 18.8%, and 100% response was observed for azathioprine, dapsone, MMF, rituximab and splenectomy, respectively.

During the third therapy, for complete response, 77.8%, 100%, 100%, 33.3%, 50%, and 100% response was observed for azathioprine, dapsone, MMF, rituximab, rituximab+steroids, splenectomy, steroids, steroids azathioprine, steroids MMF, and TPA, respectively. During the third therapy, in partial response, 22.2%, 50%, 100%, 100%, and 50% the response was observed for azathioprine, MMF, rituximab, steroids, and steroids azathioprine, respectively. During the third therapy, with no response, 50%, 33.3%, and 100% responses were observed for MMF, splenectomy, and TPA, respectively.

During the fourth therapy, for complete response, 100% response was observed for each splenectomy, steroids azathioprine, and steroids dapsone. During the fourth therapy, in partial response, 100% response was observed for each azathioprine, dapsone, and MMF. There was a significant difference between the third and fourth therapy (Table 2).

Table 2: Treatment and response of chronic ITP

		THERAPY RESPONSE						P value
		COMPLETE RESPONSE		PARTIAL RESPONSE		NO RESPONSE		
		Count	Row N %	Count	Row N %	Count	Row N %	
1st THERAPY	STEROID	22	55.0%	13	32.5%	5	12.5%	0.805
	IVIG	1	50.0%	1	50.0%	0	0.0%	
2nd THERAPY	AZATHIOPRINE	11	50.0%	6	27.3%	5	22.7%	0.334
	DAPSONE	3	30.0%	4	40.0%	3	30.0%	
	MMF	0	0.0%	3	60.0%	2	40.0%	
	RITUXIMAB	0	0.0%	1	100.0%	0	0.0%	
	SPLEENECTOMY	0	0.0%	2	50.0%	2	50.0%	
3rd THERAPY	AZATHIOPRINE	7	77.8%	2	22.2%	0	0.0%	<0.0001
	DAPSONE	1	100.0%	0	0.0%	0	0.0%	
	MMF	0	0.0%	2	50.0%	2	50.0%	
	RITUXIMAB	0	0.0%	1	100.0%	0	0.0%	
	RITUXIMAB, STEROID	1	100.0%	0	0.0%	0	0.0%	
	SPLEENECTOMY	1	33.3%	0	0.0%	1	33.3%	
	STEROID	0	0.0%	1	100.0%	0	0.0%	
	STEROID, AZATHIOPRINE	3	50.0%	3	50.0%	0	0.0%	
	STEROID, MMF	1	100.0%	0	0.0%	0	0.0%	
	TPA	0	0.0%	0	0.0%	1	100.0%	
4th THERAPY	AZATHIOPRINE	0	0.0%	1	100.0%	-	-	<0.0001
	DAPSONE	0	0.0%	1	100.0%	-	-	
	MMF	0	0.0%	1	100.0%	-	-	
	SPLEENECTOMY	1	100.0%	0	0.0%	-	-	
	STEROID, AZATHIOPRI	1	100.0%	0	0.0%	-	-	
	STEROID, DAPSONE	1	100.0%	0	0.0%	-	-	

Treatment and duration of response in weeks with and without treatment of chronic ITP:

During the first therapy, the median duration of response with treatment was 4 weeks for steroids, and 0.5 weeks for IVIG. However, the median duration of response without treatment was 4 weeks in steroid and 11 weeks in IVIG. During the second therapy, the median duration of response with treatment was 26.5, 31, 0.5, 4.5, 9 and 6 weeks for azathioprine, dapsone, MMF, rituximab and splenectomy, respectively.

During the third therapy, the duration of response with treatment was 58, 4, 2.5, 2, 26, 13, 27, and 244 weeks for azathioprine, dapsone, rituximab, rituximab+ steroids, steroids, steroids azathioprine, and steroids MMF, respectively. However, the duration of response without treatment was 21 weeks for splenectomy. Finally, during the fourth therapy, the duration of response with treatment was 9, 53, 6, 48, and 26 weeks for azathioprine, dapsone, MMF, steroids azathioprine, and steroids dapsone, respectively. However, the duration of response without treatment was 154 and 4 weeks for azathioprine and splenectomy, respectively (Table 3).

Table 3: Treatment and duration of response in weeks with and without treatment of chronic ITP

		DURATION OF RESPONSE WITH TREATMENT IN WEEKS			DURATION OF RESPONSE AFTER STOPPING TREATMENT IN WEEKS		
		Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75
1st THERAPY	STEROIDS	4.00	2.00	6.00	4.00	0.00	26.00
	IVIG	0.50	0.00	1.00	11.00	11.00	11.00
2nd THERAPY	AZATHIOPRINE	26.50	1.50	62.50			
	DAPSONE	31.00	0.00	35.00			
	RITUXIMAB	0.50	0.00	1.00			
	STEROID	4.50	0.00	9.00	3.50	0.00	7.00
	MMF	9.00	4.00	19.00	0.00	0.00	26.00
	SPLEENECTOMY	6.00	3.00	6.00	13.00	0.00	74.00
3rd THERAPY	AZATHIOPRINE	58.00	38.00	101.00	14.00	13.00	50.00
	DAPSONE	4.00	4.00	4.00	193.00	193.00	193.00
	MMF	2.50	0.00	17.50			
	RITUXIMAB	2.00	2.00	2.00			
	RITUXIMAB, STEROID	26.00	26.00	26.00			
	SPLEENECTOMY				21.00	0.00	28.00
	STEROID	13.00	13.00	13.00			
	STEROID, AZATHIOPRINE	27.00	15.00	33.00	0.00	0.00	43.00
	STEROID, MMF	244.00	244.00	244.00			
	TPA						
4th THERAPY	AZATHIOPRINE	9.00	9.00	9.00	154.00	154.00	154.00
	DAPSONE	53.00	53.00	53.00			
	MMF	6.00	6.00	6.00			
	SPLEENECTOMY				4.00	4.00	4.00
	STEROID, AZATHIOPRI	48.00	48.00	48.00			
	STEROID, DAPSONE	26.00	26.00	26.00			

DISCUSSION:

The present study mainly focused on the treatment response in chronic ITP among adults interested in affordable second-line therapy agents like azathioprine, dapsone, MMF, and other drugs. The results presented in this study were based on patients treated by a single primary physician (haematologist), based on general recommendations and individual consideration of each patient's conditions. These included prior therapy, bleeding risk, platelet count, gender, age, weight, comorbidity, quality of life, and patient preference.

The mean age at presentation in our study was 36, with the majority of them in the 18-30 years age group distribution. We observed a decline in the total number of cases with a further increase in age. Only 4 patients in our study group are more than 60 years old. Our findings were similar to those of Payandeh et al.[11]

However, this contradicted a study by Bennett et al. in the United Kingdom, which showed an increase in the prevalence of chronic ITP at age.[12] Further, our study showed female preponderance in chronic ITP with a female: male ratio of 3.42: 1 (65:19). These findings were similar to observations done by Payandeh et al. [11] and Andres et al.[13]

In our study, the most common presentation in men was asymptomatic thrombocytopenia, followed by a bleed in the skin like purpura. Menorrhagia, along with minor skin or mucosal bleeds, was the commonest symptom in females. However, the clinical manifestations of ITP were varied. In studies conducted by Difino et al.[14], Portielje et al.[15], and Wong and Lee[16], the most common presentation mode was purpuric spots on the body, followed by bleeding gums in males and menorrhagia in females. These findings are similar to those observed by Neunert et al.[17,18]

Steroids were given to almost all of our patients as a first-line therapy and later whenever required. In acute settings where platelet counts need to be increased rapidly, IVIG was given along with steroids or/and thrombopoietin receptor agonists in our patients. Also, the total response observed was similar to the observations done by Provan et al.[19] Studies conducted by Portielje et al.[15] and Wong, and Lee[16] revealed remission in 67.7% and 46.7% of patients, respectively. So, our study showed steroids have high initial response rates in ITP. However, relapses are also high in the long term.

Further, dapsone therapy has shown a good total and complete response in our study group. These findings are similar to studies done by Damodar et al. [20] and Esteve et al. [21,] with overall total response rates of 61.8% and 54.8%, respectively. These studies also showed high relapse with dapsone after stopping the therapy. Also, mycophenolate mofetil (MMF) led to an overall total response of 45.4%, and all of them had a partial response. All the patients needed continuation of therapy for the maintenance of remission. In our study, MMF had a lower response rate when compared to other treatment modalities. Studies by Taylor et al. [22] and Colovic et al. [23] have shown an overall total response of 52% and 69%, respectively. Splenectomy has shown the highest response rate and low relapse rate in our study group compared to other treatment modalities. A retrospective analysis done by Vianeli N et al. [24] showed a similar response rate (86%), and 75% of patients among responders had a durable remission. Rituximab was also used in very limited patients, given its affordability.

CONCLUSION

According to our study, we can conclude that a female preponderance of chronic ITP and thyroid disorders were the most common comorbidity. However, most of our patients didn't have any comorbidity. Menorrhagia was the most common presenting complaint among females, whereas asymptomatic thrombocytopenia was the commonest among males. Further, steroids were the most commonly used first-line agents with good initial response rates but relapses can occur in the long term. IVIG, with steroids or/ and thrombopoietin receptor agonists, produced faster responses in acute settings. Among the second-line agents, the most commonly used drugs were azathioprine, dapsone, and MMF. Of them, azathioprine and dapsone had good initial response rates but had higher relapse rates or continuation of therapy for maintenance of remission when compared to steroids. MMF had a comparatively low response rate. Because of cost restraints and availability, Rituximab and TPO receptor agonists were used in very limited cases. Splenectomy has shown the highest initial response rate and lowest relapse rate of all treatment modalities.

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