

## IMMUNE THROMBOCYTOPENIC PURPURA IN ADULTS IN THE LAST 10 YEARS: SINGLE-CENTRE EXPERIENCE

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**Abstract:** *Background:* Immune thrombocytopenic purpura (ITP) is a benign disease with low morbidity and mortality and frequent remissions that occur spontaneously or in response to first-line treatment with steroids or splenectomy.

*Aim:* The purpose of this study is to describe the clinical outcomes of 170 patients with ITP diagnosed and/or treated in our hospital between 2000 and 2010.

*Methods and results:* The median age at diagnosis was 47 years. Forty three (25%) were asymptomatic, 65% had minor skin or mucosal bleeding and 10% had significant bleeding from the gastrointestinal or genitourinary system. The median platelet count at diagnosis was  $13 \times 10^9/L$  (range:  $0-98 \times 10^9/L$ ). Median follow-up of all patients was 13 months. Ninety-five patients had a follow-up longer than 12 months, with median 44 months (range 14–384). Corticosteroids were the initial treatment for 161/170 (95%) patients, 38 (22%) were splenectomized, 25 (14.7%) were treated with intravenous gamma globulins, while 9 did not received any specific treatment. A complete response to initial treatment (prednisone  $\pm$  splenectomy) was achieved in 55/161 (34.2%), a partial response in 90 (55.9%) and no response in 16 (9.9%) patients. In the group of patients with follow-up longer than 1 year; 28 (29%) patients had refractory or unresponsive ITP with a median follow-up of 66 months. All patients with refractory ITP were treated with steroids, 11 were splenctomized, significantly more patients with refractory ITP 12 (43%) were treated with IVIG compared with other ITP patients (16%),  $p = 0.005$ . The median age of 38 splenectomized patients was 28 years and it is significantly different from the other patients ( $p < 0.001$ ). There were no significant differences in other characteristics between splenctomized or refractory ITP and other patients at diagnosis.

*Conclusion:* Our results were similar to results already reported in other similar studies.

**Key words:** immune thrombocytopenic purpura, corticosteroids, splenectomy.

### *Background*

Immune thrombocytopenic purpura (ITP) is an autoimmune disease of unknown etiology, characterized by thrombocytopenia due to the presence of platelet autoantibodies specific for platelet membrane glycoproteins, such as GPIIb/IIIa, GPIb/IX and GPIa/IIa [1]. These autoantibodies cause an accelerated destruction of autoantibody-opsonized platelets by Fc $\gamma$ Receptor bearing phagocytic cells in the reticuloendothelial system, or inhibition of platelet production [2]. The etiology of ITP remains unclear, but both genetic and environmental factors are thought to play a role in the development of the disease. Several genes involved in immune system regulation such as cytokine genes [3, 4], Fc gamma receptor genes [4, 5], CTLA-4 gene [6], and HLA genes [7], as well as some infective agents such as hepatitis C virus, HIV virus, and helicobacter pylori [8–10] have been associated with susceptibility to ITP in several studies.

Two forms of the disease exist: acute ITP, predominantly occurring in children, and the chronic form which is commonly seen in adults. In children, the disease is often self-limiting within a 6-month period and is commonly associated with infection. In adults, ITP is more often a chronic disease and has an insidious onset, spontaneous remissions are rare and therapy with corticosteroids and splenectomy is commonly required [11]. Results from some long-term follow-up series suggest that ITP is a more benign disease and should be treated by a conservative approach, reserving aggressive treatment for patients with severe and symptomatic thrombocytopenia [12–14]. The annual incidence is nearly 30 new cases per 1 million [15]. The diagnosis of ITP is based on clinical features, complete blood count and exclusion of other causes of thrombocytopenia [16]. Bleeding symptoms are rare unless the thrombocytopenia is severe (platelet count  $< 30 \times 10^9/L$ ) [16].

There have been few randomized controlled trials analysing the incidence, investigation and management of patients with ITP [14, 17, 18]. The aim of our study was to evaluate 170 patients diagnosed and treated with ITP in our institution in the last 10 years (between 2000 and 2010).

### *Methods*

The institution database was analysed for patients diagnosed and/or treated for ITP between 2000 and 2010. We analysed retrospectively 170 cases referred to our hospital in that period. All patients met the diagnostic criteria for ITP a) platelet count below  $100 \times 10^9/L$  in peripheral blood, b) normal or increased megakaryopoiesis on bone marrow examination, and c) the absence of clinically apparent associated conditions or causes of thrombocytopenia. The

medical records of these patients were reviewed for the clinical and laboratory information regarding their diagnosis, initial treatment, splenectomy and after treatment follow-up. The severity of thrombocytopenia was classified into: severe (platelets  $< 30 \times 10^9/L$ ); moderate (platelet count  $30\text{--}50 \times 10^9/L$ ) and mild (platelets  $> 50 \times 10^9/L$ ). Data collected from medical records were age at diagnosis, gender, symptoms and type of bleeding, platelet count at diagnosis, platelet count after treatment and at last recorded check-up, treatment modality, splenectomy and time of follow-up after splenectomy in months, and response to different treatments. The data were analysed using the standard statistical test in Microsoft Office Excel 2003.

### *1. Therapy and definitions of response*

First-line treatment consisted of oral prednisone (1mg/kg/d) for 3–6 weeks, followed by a tapering-off period of maximally 1 year with subsequent withdrawal. Indications for splenectomy were no platelet response after at least 6 weeks of prednisone, one or more recurrences after withdrawal of prednisone, or requirement of maintenance prednisone treatment ( $> 0.10$  mg/kg). Second-line treatment was given if no response occurred after splenectomy. Most commonly prednisone was reintroduced in therapy or other immunosuppressive therapies were used (azathioprine, cyclophosphamide, rituximab). Intravenous gamma globulins (IVIG) were reserved for interventions during serious bleeding episodes or to raise the platelet count before splenectomy or other surgery (delivery).

The response criteria to treatment were defined as: complete response (CR), as platelet counts  $> 100 \times 10^9/L$ ; partial response or response (R) according Rodighiero et al. [19] as platelet counts  $> 30 \times 10^9/L$  and at least doubling of the baseline count; and no response (NR) as platelet count of less than  $30 \times 10^9/L$  with or without therapy [19]. The same criteria were used to define CR and R after splenectomy. No response to splenectomy was defined as a platelet count below  $30 \times 10^9/L$  at any time after splenectomy and requirement of additional therapy. Relapse after splenectomy was defined as a decrease in platelet counts below  $30 \times 10^9/L$ . Response to initial therapy was defined as response to treatment with prednisone  $\pm$  splenectomy. Refractory ITP was defined as a platelet count lower than  $30 \times 10^9/L$  despite treatment with a standard dose of corticosteroids and splenectomy. According to the latest recommendations by Rodighiero et al. patients with refractory ITP must fail splenectomy. But in our country splenectomy is often avoided or delayed and a significant number of ITP patients are not candidates for splenectomy due to advanced age and concomitant disease, so we used the term "refractory ITP" not only for patients who failed splenectomy but also for unsplenectomized ITP patients who are unresponsive to one or more agents.

## Results

### 1. Characteristics of patients at diagnosis

The median age at diagnosis was 47 years (range 14–83 years). Forty-six 46/170 (27%) were males and 124/170 (73%) were females (Table 1). Forty-three (25%) were asymptomatic, 110 (65%) had minor skin or mucosal bleeding and 17/170 (10%) had significant bleeding from the gastrointestinal or genitourinary system. None of the patients had severe, life-threatening bleeding symptoms. The median platelet count at diagnosis was  $13 \times 10^9/L$  (range:  $0-98 \times 10^9/L$ ), the number of patients with severe thrombocytopenia was 125/170 (74%), with moderate thrombocytopenia 24 (14%) and with mild 21 (12%). Bleeding symptoms were more common in patients with severe thrombocytopenia, 108/125 (86.4%) patients compared to patients (11/24 = 45.8%) with moderate and 8/21 pts (38%) with mild thrombocytopenia ( $p < 0.001$ ,  $\chi^2 = 34.5$ ). Bone marrow examination was performed in 129/170 (76%) of patients. Anti-platelet antibodies were positive in 8/35 (23%) and negative in 27/35 (77%) patients. A direct antiglobuline test (DAT or Coombs test) was positive in 7/135 (5.2%) patients and 4/135 (2.9%) patients had hemolytic anemia (Fisher Evans Syndrome). Median follow-up of all patients was 13 months (range 3–384 months). Ninety-five ( $n = 95$ ) patients had a follow-up longer than 12 months, with median 44 months (range 14–384). There was no significant difference between these two groups of patients. Splenectomized patients were 38 with a median age 28 years (range 14–57), which was significantly different from the other two groups of patients ( $p < 0.001$ ). There were no significant differences in other characteristics between splenectomized and other patients (Table 2).

Corticosteroids were the initial treatment for 161/170 (95%) patients, 38 pts (22%) were splenectomized, 25 patients (15%) were treated with intravenous gamma globulins (IVIg), while 9 pts did not received any specific treatment due to mild, asymptomatic thrombocytopenia. A complete response to initial treatment (prednisone  $\pm$  splenectomy) was achieved in 55/161 pts (34.2%), partial response in 90/161 (55.9%) and no response in 16/161 (9.9%) patients. The median platelet count at the last control was  $161 \times 10^9/L$  (range:  $2-704 \times 10^9/L$ ). At the last follow-up, the number of patients with severe thrombocytopenia was 12/170 (7.1%), with moderate thrombocytopenia 12 (7.1%), with mild 33 (19.4%) and with platelet count  $> 100 \times 10^9/L$  it was 113/170 (66.4%). At the last control 79 out of 170 (46.5%) patients were without therapy for ITP, 64 (37.6%) were still receiving prednisone, 16 (9.4%) azathioprine, 9 (5.3) both low doses of prednisone and azathioprine, and 2 patients were treated with cyclophosphamide. During the follow-up, antinuclear antibodies were diagnosed in four patients, and malignant disease in two patients (1 with breast cancer and 1 with metastatic carcinoma).

Table 1

*Patients characteristics at diagnosis*

Characteristics	N = 170	%
Age(years), median (range)	47 (14–83)	
Gender		
Male	46	27%
Female	124	73%
Clinical presentation		
No haemorrhagic symptoms	43	25%
Haemorrhagic symptoms		
Skin or mucosal bleeding	110	65%
GIT or genital bleeding	17	10%
Platelet count at diagnosis, median (range)	$13 \times 10^9/L$ ( $0-98 \times 10^9/L$ )	
<b>Thrombocytopenia</b>		
Severe (Plt $< 30 \times 10^9/L$ )	125	74%
Moderate (Plt $30-50 \times 10^9/L$ )	24	14%
Mild (Plt $> 50 \times 10^9/L$ )	21	12%
Median follow-up in months (range)	13 (3–384)	
Bone-marrow examination	129	76%
Anti-platelet antibodies	8/35	23%
DAT	7/135	5.2%
AIHA	4/135	2.9%
Platelet count at last control, median (range)	$161 \times 10^9/L$ ( $2-704 \times 10^9/L$ )	
<b>Thrombocytopenia</b>		
Severe (Plt $< 30 \times 10^9/L$ )	12	7.1%
Moderate (Plt $30-50 \times 10^9/L$ )	12	7.1%
Mild (Plt $> 50 \times 10^9/L$ )	33	19.4%
Normal (Plt $> 100 \times 10^9/L$ )	113	66.4%
Treatment		
<b>First line treatment</b>		
Prednisone	161	95%
No therapy	9	5%
<b>Second line treatment</b>		
Splenectomy	38	22%
IVIg	25	15%
Other	51	32%
(azathioprin, cyclophosphamide, rituximab)		
Response to initial treatment (Prednisone $\pm$ Splenectomy) n = 161		
CR	55/161	34.2%
R	90/161	55.9%
NR	16/161	9.9%

When we selected patients with a follow-up longer than 1 year ( $n = 95$ ), the median age at diagnosis was 47 years (range 14–81 years); 27 (28%) were males and 68 (72%) were females (Table 2). Twenty-four (25.3%) were asymptomatic, 63 (66.3%) had minor skin or mucosal bleeding and 8 (8.4%) had significant bleeding from the gastrointestinal or genitourinary system. The median platelet count at diagnosis was  $16 \times 10^9/L$  (range:  $0-91 \times 10^9/L$ ). The number of patients with severe thrombocytopenia was 69 (72%), with moderate thrombocytopenia 15 (16%) and with mild 11 (12%). Bone-marrow examination was performed in 73 (77%) of patients. These 95 patients had a follow-up longer than 12 months, with a median of 44 months (range 14–384). Corticosteroids were the initial treatment for 89 (94%) patients, 34 (36%) were splenectomized, 15 (16%) were treated with intravenous gamma globulins (IVIG), while 6 (6%) pts did not receive any specific treatment due to mild, asymptomatic thrombocytopenia. A complete response to initial treatment (prednisone  $\pm$  splenectomy) was achieved in 39 (43.8%) patients, partial response in 40 (45%) and no response in 10 (11.2%) patients. The median platelet count at the last control was  $137 \times 10^9/L$  (range:  $2-704 \times 10^9/L$ ). At the last follow-up, the number of patients with severe thrombocytopenia was 11 (11.6%), with moderate thrombocytopenia 8 (8.4%), with mild 18 (18.9%) and with platelet count  $> 100 \times 10^9/L$  it was 58 (61.1%). At the last control 58 (61%) patients were without therapy for ITP, 37 (39%) were still receiving therapy.

In the group of patients with a follow-up longer than 1 year; 28 (29%) patients had refractory or unresponsive ITP, while 11 (29%) splenectomized patients had refractory ITP. The median follow-up of patients with refractory ITP was 66 months (range: 12–384), 21 were female and 7 male. All patients were treated with steroids, 11 were splenectomized, significantly more patients with refractory ITP 12 (43%) were treated with IVIG due to serious hemorrhagic syndrome or to a raised platelet count before splenectomy or other surgical intervention compared with other ITP patients (16%),  $p = 0.005$  with Yates correction. Ten patients were receiving azathioprine, two cyclophosphamide and two rituximab. There were significantly more patients with severe or moderate thrombocytopenia at the last control, between refractory and other ITP patients,  $p < 0.001$  (Table 2). There were no other significant differences between refractory and other ITP patients at diagnosis.

Table 2

*Characteristics of patients followed longer than 12 months, splenectomized patients and patients with refractory or unresponsive ITP*

Characteristics	N = 95 (follow-up > 12 mo)	N = 38 (splenectomy)	N = 28 (unresponsive)	P- value
Age(years), median (range)	47 (14–81)	28 (14–57)	42 (14–73)	< <b>0.001</b>
Gender				
Male	27 (28%)	9 (24%)	7 (25%)	
Female	68 (72%)	29 (76%)	21 (75%)	0.834 <sup>#</sup>
Clinical presentation				
No haemorrhagic symptoms	24 (25.3%)	7 (18.4%)	4 (14.3%)	
Haemorrhagic symptoms				
Skin or mucosal bleeding	63 (66.3%)	27 (71%)	20 (71.4%)	0.671
GIT or genital bleeding	8 (8.4%)	4 (10.6%)	4 (14.3%)	
Platelet count at diagnosis				
median (range)	16 × 10 <sup>9</sup> /L (0–91 × 10 <sup>9</sup> /L)	18 × 10 <sup>9</sup> /L (0–91 × 10 <sup>9</sup> /L)	18 × 10 <sup>9</sup> /L (2–56 × 10 <sup>9</sup> /L)	
Severe (Plt < 30 × 10 <sup>9</sup> /L)	69 (72%)	28 (74%)	24 (85.8%)	
Moderate (Plt 30–50 × 10 <sup>9</sup> /L)	15 (16%)	7 (18%)	2 (7.1%)	0.619
Mild (Plt > 50 × 10 <sup>9</sup> /L)	11 (12%)	3 (8%)	2 (7.1%)	
Platelet count at last control				
median (range)	137 × 10 <sup>9</sup> /L (2–704 × 10 <sup>9</sup> /L)	240 × 10 <sup>9</sup> /L (15–704 × 10 <sup>9</sup> /L)	48 × 10 <sup>9</sup> /L (2–137 × 10 <sup>9</sup> /L)	
Thrombocytopenia				
Severe (Plt < 30 × 10 <sup>9</sup> /L)	11 (11.6%)	1 (2.6%)	9 (32%)	
Moderate (Plt 30–50 × 10 <sup>9</sup> /L)	8 (8.4%)	2 (5.3%)	6 (22%)	< <b>0.001</b> <sup>I</sup>
Mild (Plt > 50 × 10 <sup>9</sup> /L)	18 (19%)	7 (18.4%)	9 (32%)	0.328 <sup>2</sup>
Normal (Plt > 100 × 10 <sup>9</sup> /L)	58 (61%)	28 (73.7%)	4 (14%)	
Median follow-up in months (range)	44 (14–384)	43 (3–384)	61 (12–384)	
Treatment				
First line treatment				
Prednisone	89 (94%)	38 (100%)	28 (100%)	
No therapy	6 (6.3%)	0 (0%)		
Second line treatment				
Splenectomy	34 (36%)	38 (100%)	11 (39%)	
IVIG	15 (16%)	12 (31.6%)	12 (43%)	
Other	32 (34%)	14 (37%)	14 (50%)	
Response to initial treatment (Prednisone ± Splenectomy)				
	n = 89	n = 38	n = 28	
CR	39 (43.8%)	20 (52.6%)	11 (39.3%)	
R	40 (45%)	10 (26.4%)	10 (35.7%)	0.168 <sup>I</sup>
NR	10 (11.2 %)	8 (21%)	7 (25%)	
Refractory ITP	28 (29%)	11 (29%)		

\* (azathioprin, cyclophosphamide, rituximab); <sup>#</sup> With Yates' correction; <sup>I</sup> P-value between all three groups; <sup>2</sup> P-value between 1<sup>st</sup> and 2<sup>nd</sup> group

*Discussion*

A recent population-based study suggests that adult chronic ITP is a more benign disease than previously suspected, with a low morbidity and mortality risk and frequent remissions that occur spontaneously or in response to first-line treatment with steroids [13, 14, 20]. Several studies show a response to initial corticosteroid treatment in 60–70% of patients who require therapy, but only 20–30% of treated patients have a sustained complete remission lasting more than a year after discontinuation of maintenance therapy [12, 14]. Due to these results patients with mild and asymptomatic thrombocytopenia should not be treated unless they have a risky lifestyle (sports, etc), need for surgery or other invasive procedures or are at higher risk of bleeding because of associated conditions such as hypertension, cerebrovascular disease, anticoagulant therapy [21–23]. However, a substantial number of patients, 20–30%, have a refractory and chronic form of the disease, characterized by severe thrombocytopenia that requires permanent treatment. Management of these patients refractory to standard treatment with corticosteroids and splenectomy is difficult, because the response rate to all available treatments at the moment is low and not long-lasting [12, 17, 24].

Our retrospective study describes the clinical outcomes of 170 patients with ITP diagnosed and/or treated in our hospital in the period between 2000 and 2010. This is the first study of this type in Macedonia and our results are similar to the results from other studies analysing clinical outcomes and characteristics of patients with ITP. Ninety-five (56%) patients had a follow-up period longer than 1 year with a median of 44 months (range: 12–384), while 75 other patients had acute ITP associated with infections ( $n = 9$ ), 36 patients were diagnosed in the years 2009 and 2010 and had a follow-up period of less than 12 months. After the initial diagnosis and treatment, a significant number of these 170 patients  $n = 30$  (17%), did not have check-ups in our hospital, for unknown reasons, so we do not have data on their medical conditions at the moment of this study. This study does not give an exact picture of the incidence and outcomes of patients with ITP in our country, mostly due to the fact that we are a tertiary centre. Probably a significant number of patients with mild thrombocytopenia are not referred to our hospital and/or continue with medical check-ups after diagnosis and treatment in local medical institutions. But most of the patients with chronic and refractory ITP continue to come to our hospital, so the present data are useful in an analysis of the clinical course and treatment of this group of patients. The ideal study to analyse ITP would be a population-based study from a defined medical region, but such a study would be difficult to conduct due to the large number of patients required and the long follow-up.

Results from our study are similar to those previously reported with regard to median age (47 years; range: 14–83), sex distribution, haemorrhagic



symptoms, platelet counts, etc (Table 3). the response rate to initial treatment with steroids and splenectomy was high, 88% (Table 2), with CR in 43% and R in 45% of patients, but the sustained response was lower due to the drop in the platelet count during steroid tapering and relapses. In the group of patients with a follow-up longer than 1 year; 28 (29%) patients had refractory ITP. Similar response rates were reported by McDonald [25] with CR in 35%, R in 48% and NR in 17 % and Stasi et al. [12] with CR in 46 (38.8%). Portielje et al. [14] reported CR in 59%, R in 16% and NR in 8% of ITP patients. This higher response rate in the study of Portielje et al. [14] could be explained by a higher percentage of splenectomized patients 70 (46%) compared to 38 (22%) in our group of patients with ITP (Table 3). Differences in the response rates between different studies could be explained by different response criteria and a different time of evaluation of response. The evaluation period in our study and in the study of Stasi

Table 3

*Patients' characteristics and outcomes in our and two other studies*

Characteristics	Pavkovic	Portielje [14]	McDonald [25]
	n = 170 (%) Macedonia	n = 152 Netherland	n = 67 New Zealand
Age(years), median (range)	47 (14–83)	41 (15–)85	/
Gender			
Male	46 (27)	56 (37)	/
Female	124 (73)	96 (63)	/
Clinical presentation			
No haemorrhagic symptoms	43 (25)	28 (18)	57* (85)
Haemorrhagic symptoms		124 (82)	10 <sup>#</sup> (15)
Skin or mucosal bleeding	110 (65)	89 (58)	/
GIT or genital bleeding	17 (10)	32 (21)	/
Thrombocytopenia			
Severe <sup>1</sup>	125 (74)	124 (82)	29 (55)
Moderate <sup>2</sup>	45 (26)	28 (18)	24 (45)
Response to initial treatment (Prednisone ± Splenectomy)			
CR	161/38	152/70	52/17
R	55/161 (34.2)	90 (59)	18(35)
NR	90/161 (55.9)	24 (16)	25 (48)
Death	16/161 (9.9)	12 (8)	9 (17)
Secondary ITP	0	4 (0.02)	0
No therapy	/	12 (8)	/
	9/170 (5.3)	13 (8.5)	/

\* mildly symptomatic or asymptomatic; <sup>#</sup> symptomatic

<sup>1</sup> (Plt < 30 × 10<sup>9</sup>/L); <sup>2</sup> (Plt > 30–100 × 10<sup>9</sup>/L)

et al. [12] was 6 months after treatment, while in the study of Portielje et al. it was 2 years after diagnosis. The low response rate in our study could also be explained by a low percentage of splenectomized patients and postponing splenectomy to later in the course of disease. Macedonia is a developing country with a relatively lower educational level of the population and that could be the reason for the refusal of splenectomy as a therapeutical procedure by a significant number of patients. That could also be a reason for lower therapy compliance in our population compared with more developed European countries.

The median follow-up of our patients with unresponsive or refractory ITP was much longer, 66 months (range: 12–384). Patients with refractory ITP were resistant to 2 or more therapeutical options, 11 of them were splenectomized, 2 were treated with rituximab, 2 with cyclophosphamide, and all of them are on continuous or temporary treatment with corticosteroids. Only 4 (14%) of them had a platelet count  $> 100 \times 10^9/L$  at the last control and 9 (32%) were without therapy at the time of the last check-up. Fortunately, we had no deaths connected to ITP or its treatment, similar to McDonald [25], while Stasi [12] reported 5/208 (0.02) deaths as did Portielje, [14] who reported 4 deaths, one due to haemorrhage and 3 due to infection (Table 3).

In conclusion, our results proved that most adults with ITP have a good outcome, with low morbidity and mortality. But almost 30% of patients who have been monitored more than 1 year in our study have a chronic unresponsive or refractory form of ITP, which represents a significant medical problem due to the constant need for treatment and frequent controls.

#### *Declaration of Interest*

We disclose any financial relationship with any biotechnological or pharmaceutical company and there is no conflict of interest.

#### REFERENCES

1. McMillan R. Chronic idiopathic thrombocytopenic purpura. *N Eng J Med.* 1981; 304: 1135.
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Eng J Med.* 2002; 346: 995–1008.
3. Satoh T, Pandey JP, Okazaki Y, et al. Single nucleotide polymorphisms of the inflammatory cytokine genes in adults with chronic immune thrombocytopenic purpura. *Br J Haematol.* 2004; 124: 796–801.
4. Foster CB, et al. Polymorphisms in inflammatory cytokines and Fcγ receptors in childhood chronic immune thrombocytopenic purpura: a pilot study. *Br J Haematol.* 2001; 1134: 596–599.

5. Breunis WB, van Mirre E, Bruin M, Geissler J, Boer M, Peters M, Roos D, Haas M, Koene HR, Kuijpers TW. Copy number variation of the activating FCGR2C gene predisposes to idiopathic thrombocytopenic purpura. *Blood*. 2008; 111: 1029–1038.
6. Pavkovic M, Georgievski B, Cevreska L, Spiroski M, Efremov DG. CTLA-4 Exon 1 Polymorphism in patients with autoimmune blood disorders. *Am J Hematol*. 2003; 72: 147–9.
7. Kuwana M, Kaburaki J, Pandey JP, Murata M, Kawakami Y, Inoko H, Ikeda Y. HLA class II alleles in Japanese patients with immune thrombocytopenic purpura. Associations with anti-platelet glycoprotein autoantibodies and responses to splenectomy. *Tissue Antigens*. 2000; 56: 337–343.
8. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*. *Lancet*. 1998; 352: 878.
9. Kuwana M, Ikeda Y. *Helicobacter pylori* and immune thrombocytopenic purpura: unsolved questions and controversies. *Int J Hematol*. 2006; 84: 309–15.
10. Satoh T, Pandey JP, Okazaki Y, et al. Single nucleotide polymorphisms of interleukin-1 $\beta$  associated with *Helicobacter pylori* infection in immune thrombocytopenic purpura. *Tissue Antigens*. 2009; 73: 353–357.
11. George JE, Woolf SH, Raskob GE, Wasser JS, Alderot LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996; 88: 3–40.
12. Stasi R, Stipa E, Masi M, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. *Am J Med*. 1995; 98: 436–442.
13. Neylon AJ, Saunders PW, Howard MR, Proctor S, Taylor PR. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population based cohort of 245 patients. *Br J Haematol*. 2003; 122: 966–974.
14. Portielje JE, Westendorp RG, Kluin-Nelmand HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood*. 2001; 97: 2549–54.
15. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. *Blood*. 1999; 94: 909–913.
16. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol*. 2003; 120: 574–96.
17. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood*. 2004; 104: 956–960.
18. Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *J Throm Haemos*. 2006; 4: 2377–2383.

19. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, 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: 2386–2393.
20. Cohen YC, Djulbegovic B, Shami-Lubovitz O, Mozes B, et al. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med*. 2000; 160: 1630–1638.
21. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura in adults. *Semin Thromb Hemost*. 1977; 3: 160–174.
22. Cortelazzo S, Finazzi G, Buelli M, et al. High-risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. *Blood*. 1991; 77: 31–33.
23. Guthrie TH, Brannan DP, Pristant LM. Idiopathic thrombocytopenic purpura in the older adult patient. *Am J Med Sci*. 1988; 296: 17–21.
24. Bourgeois E, Caulier MT, Delarozee C, et al. Long term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. *Br J Haematol*. 2003; 120: 1079–1088.
25. McDonald EJ, Butler A. Immune thrombocytopenia in adults: a single-centre retrospective review of patients presenting over 7 years. *N Z Med J*. 2010; 123: 18–25.

#### Резиме

### **ИДИОПАТСКА ТРОМБОЦИТОПЕНИЧНА ПУРПУРА КАЈ ВОЗРАСНИ ВО ПОСЛЕДНИТЕ 10 ГОДИНИ: ИСКУСКУТВА НА НАШИОТ ЦЕНТАР**

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Имуната тромбоцитопенична пурпура (ИТП) е автоимуно заболување кое се карактеризира со тромбоцитопенија која се должи на присуството на анти-тромбоцитни автоантитела. Хроничната ИТП кај возрасните е во основа бенигно заболување, со низок морбидитет и морталитет, со чести ремисии кои настапуваат спонтано или по прволиниска терапија со кортико-стероиди или спленектомија.

Оваа студија го прикажува клиничкиот тек и исход на 170 пациенти дијагностицирани и/или лекувани од ИТП во нашата установа во периодот од 2000–2010 година. Медијана на возраста при дијагностицирање беше 47

години. Четириесет и три (25%) пациенти немаа симптоми, 65% имаа минорни кожни или мукозни крвавења и 10% болни имаа крвавења од гастроинтестиналниот или урогениталниот тракт. Ниту еден пациент немаше тешки, живото-загрозувачки крвавења. Медијана на бројот на тромбоцитите при дијагностицирањето беше  $13 \times 10^9/L$  (ранг:  $0-98 \times 10^9/L$ ). Медијана на следење на болните беше 14 месеци (3-384). Деведесет и пет болни беа следени подолго од 12 месеци, со медијана од 44 месеци (ранг 12-384). Кортикостероидите беа иницијален третман кај 161/170 (95%) болни, 38 (22%) беа спленектомирани, 25 (15%) беа лекувани со интравенски гамаглобулини, 9 болни не беа лекувани поради блага, асимптоматска тромбоцитопенија. Комплетен одговор на иницијалната терапија (преднизон  $\pm$  спленектомија) беше постигнат кај 55/161 (34,2%), парцијален одговор кај 90 (55,9%) додека без одговор беа 16 (9,9%) болни. Во групата на болни со следење подолго од 12 месеци; 28 (29%) од болните имаа рефрактерна ИТП со медијана на следење од 66 месеци. Сите пациенти со рефрактерна ИТП беа лекувани со кортикостероиди, 11 беа спленектомирани, значително поголем број болни со рефрактерна ИТП 12 (43%) беа лекувани со ИВИГ во споредба со останатите,  $p = 0,005$ . Десет болни беа лекувани со азатиоприн, 2 со циклофосфамид и два со ритуксимаб. Медијана на возраста на спленектомираните болни беше 28 години и сигнификантно се разликуваше од останатите болни ( $< 0,001$ ). Сигнификантно помал број болни со рефрактерна ИТП (14%) имаа нормален број на тромбоцити при последната контрола во споредба со останатите пациенти,  $p < 0,001$ . Немаше други статистички значителни разлики меѓу спленектомираните или болните со рефрактерна ИТП и останатите болни.

**Клучни зборови:** имуна тромбоцитопенична пурпура, кортикостероиди, спленектомија.

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