



Clinical course and prognostic factors of childhood immune thrombocytopenia: single center experience of 10 years

Jae Yeob Jung, MD, A Rum O, MD, Je Keong Kim, MD, Meerim Park, MD, PhD

Department of Pediatrics, Chungbuk National University College of Medicine, Cheongju, Korea

Purpose: This study aimed to evaluate the clinical course of childhood immune thrombocytopenia (ITP) and to assess the risk factors for developing chronic ITP

Methods: The records of 64 children diagnosed with ITP from November 2005 and December 2014 at single center were retrospectively analyzed.

Results: The median age at diagnosis and the median platelet count were 1 year (range, 1 month to 15 years) and $9 \times 10^9/L$ (range, $0-84 \times 10^9/L$), respectively. No patient experienced severe bleeding. Nineteen children (29.7%) spontaneously recovered their platelet count to $\geq 100 \times 10^9/L$ at a median of 10 days. In total 45 patients (70.3%) received intravenous immunoglobulin (IVIG) as first-line therapy, and showed platelet recovery at 1 week. The final diagnosis of 55 (85.9%) and 9 patients (14.1%) was acute and chronic ITP, respectively. Older age, absence of prior infection and insidious onset of symptoms were significantly associated with the development of chronic ITP. Among the patients who received IVIG, those with platelet count $< 45 \times 10^9/L$ at 1 month after IVIG showed a significantly higher incidence of chronic ITP compared to those with platelet count $\geq 45 \times 10^9/L$ (88.8% vs. 44.4%, $P < 0.01$).

Conclusion: In most patients, ITP runs a benign course and approximately 86% of them recover within 1 year of their initial diagnosis. The potential impact of the risk factors of chronic ITP on clinical practice needs to be explored and further studies are warranted to determine whether IVIG influences the course of ITP.

Key words: Immune thrombocytopenia, Acute, Chronic

Corresponding author: Meerim Park, MD, PhD
Department of Pediatrics, Chungbuk National University College of Medicine, Chungdae-ro 1, Seowon-Gu, Cheongju 28644, Korea
Tel: +82-43-269-6338
Fax: +82-43-264-6620
E-mail: ming2a@daum.net

Received: 3 May, 2016
Revised: 17 July, 2016
Accepted: 28 July, 2016

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts due to immunologic destruction of normal platelets and suboptimal platelet production. The International Working Group (IWG) defines ITP as a platelet count less than $100 \times 10^9/L$ in the absence of other secondary causes. In children, ITP typically presents in otherwise healthy patients, often resolving spontaneously or following therapy within 6–12 months of diagnosis. However, approximately 20%–25% of children with newly diagnosed ITP ultimately develop chronic disease, defined as persistent thrombocytopenia lasting for > 12 months¹. While prior investigations have identified several risk factors associated with the development of chronic ITP, both the natural course of ITP and the risk of life-threatening bleeding remain difficult to predict for individual patients².

Due to the considerable impact of ITP on a child's everyday life and activities, the ability to predict clinical course at the time of diagnosis could potentially reduce morbidity and assist in guiding therapy. Thus, the purpose of this study was to further evaluate the clinical

Copyright © 2016 by The Korean Pediatric Society

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

course of childhood ITP and to assess previously described risk factors for developing chronic ITP. Finally, for patients treated with intravenous immunoglobulin (IVIG), we investigated the performance of platelet counts at 1 month following therapy as a predictor of subsequent disease course.

Materials and methods

1. Study population and demographics

The records of ITP patients with a platelet count less than $100 \times 10^9/L$ between November 2005 and December 2014 at the Department of Pediatrics, Chungbuk National University Hospital were retrospectively reviewed. We excluded patients with secondary causes of thrombocytopenia such as medications, systemic lupus erythematosus, viral hepatitis, human immunodeficiency virus, hematologic malignancy, bone marrow failure, and von Willebrand disease. For patients <3 months old, we excluded patients born from mother with thrombocytopenia in order to avoid inclusion of patients with thrombocytopenia secondary to maternal allo- or auto-antibodies.

Patient age at the time of diagnosis was recorded, and stratified as follows: age <100 days, age between 100 days and 1 year, age 1–10 years, or age ≥ 10 years. Records were reviewed for gender, history of antecedent infection or recent vaccination 2 weeks prior to diagnosis.

2. Presentation and clinical characteristics

Disease onset was characterized and recorded as abrupt (duration of symptoms <14 days at presentation) or insidious (symptoms for ≥ 14 days at presentation)³. We also recorded the incidence of bleeding manifestations; bleeding symptoms were classified as mild, moderate or severe⁴. Mild symptoms were limited to bruises and petechiae in the absence of mucosal bleeding. Moderate symptoms were defined as mucosal bleeding (such as epistaxis or gum bleeding) that did not require medical intervention. Severe symptoms included mucosal bleeding requiring immediate medical intervention (including blood transfusion), suspected or documented intracranial hemorrhage (ICH), and other life-threatening or fatal hemorrhage in any site.

Laboratory values included platelet counts, white blood cell (WBC) counts, hemoglobin, % of lymphocytes, and % of eosinophils. Initial and follow-up values were compared. For patients who received treatment, we recorded platelet values following therapy, including values obtained 1, 3, 6, and 12 months following treatment to assess response to treatment.

IVIG was administered at a dose of 1 g/kg for 2 consecutive days as initial treatment for patients with platelet counts $\leq 20 \times 10^9/L$ or moderate to severe bleeding symptoms as defined above. Platelet count $\leq 20 \times 10^9/L$ was chosen as the treatment threshold

for the following reasons: serious bleeding is more frequent below this level, and national health insurance coverage IVIG requires platelet counts $\leq 20 \times 10^9/L$. Adopting IWG proposed criteria, we assessed treatment response as follows: complete response (CR) as any platelet count $> 100 \times 10^9/L$; partial response (PR) as any platelet count between 30 and $100 \times 10^9/L$ and doubling of the baseline count; and no response (NR) as any platelet count $< 30 \times 10^9/L$ or less than doubling of the baseline count⁵. Additionally, any adverse effects related to treatment were recorded according to Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

Following initial presentation and management, the children with ITP were followed as outpatients by an attending hematologist for a period of at least 12 months or until resolution of disease. The new terms “newly diagnosed” and “persistent” replaced the previous term “acute” for children diagnosed with ITP within the last 3 months and for cases lasting between 3 and 12 months from diagnosis, respectively. Chronic ITP was defined as persisting thrombocytopenia of less than $100 \times 10^9/L$ lasting for more than 12 months⁶.

3. Statistical analysis

Data were analyzed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Subgroups of patients were characterized and compared using descriptive statistics. Differences in dichotomous variables were analyzed using Pearson chi-square test, while differences in continuous variables were assessed via the Mann-Whitney *U* test. WBC count, % lymphocytes, and % eosinophils were analyzed separately based on age groups defined as age <100 days, age between 100 days and 1 year, age 1–10 years, or age ≥ 10 years. *P* values of <0.05 were considered statistically significant.

Results

1. Clinical features

A total of 64 children were included in this study. The median follow-up period was 50 months (range, 12–125 months). The median age at diagnosis was 1 year (range, 1 month to 15 years); 17 patients (26.6%) with age of <100 days, 9 patients (14.1%) with age of 100 days to 1 year, 31 patients (48.4%) with age of 1 year to 10 years and 7 patients (10.9%) with age of ≥ 10 years. Thirty-nine patients (60.9%) were reported to have antecedent infection, and 9 patients (14.1%) received vaccinations <14 days before diagnosis of thrombocytopenia. Twenty-one patients (32.8%) had neither recent vaccination nor clinical evidence of recent infection. Bleeding symptoms proved predominantly mild ($n=38$), with moderate bleeding symptoms present in the minority of patients ($n=10$). However, no patients in the study developed

severe bleeding symptoms. Each of the 15 patients (23.4%) who presented without bleeding was incidentally diagnosed as thrombocytopenic during workup of antecedent infection. Median platelet count at presentation was $9 \times 10^9/L$ (range, $0-84 \times 10^9/L$). Forty patients (62.5%) initially presented with platelet counts below our established treatment cutoff of $20 \times 10^9/L$.

2. Treatment and outcome

Of the 22 patients with platelet count $>20 \times 10^9/L$ and no moderate or severe bleeding symptoms at presentation, 19 patients (86.4%) showed spontaneous recovery to platelet counts $\geq 100 \times 10^9/L$ at a median time of 10 days (range, 7-35 days). Forty-five patients (70.3%) ultimately received treatment for thrombocytopenia, the vast majority ($n=42$) upon initial presentation. The remaining 3 patients were treated at 22, 37, and 405 days, respectively, after initial presentation. IVIG was initiated as first-line therapy in all patients treated for ITP. At one week following treatment, 44 patients (97.8%) exhibited response to therapy (CR in 30 patients, PR in 14 patients). The single patient who showed NR to IVIG eventually achieved PR after reinfusion of IVIG and supplementation with high-dose steroids (intravenous methylprednisolone of 10 mg/kg/day for 3 days).

Despite initial response to therapy, 15 patients (33.3%) were eventually showed recurrent thrombocytopenia at a median of 33 days (range, 8-858 days). Eleven of these patients received repeated IVIG treatment with ($n=3$) or without ($n=8$) steroids (prednisolone with initial dose of 1 to 2 mg/kg per day orally for 5 or more days with subsequent dose tapering), yielding CR in 8, PR in 2, and NR in 1 patient. No patients underwent splenectomy during the study period. IVIG related acute complications included transient fever ($n=11$), vomiting ($n=10$), abdominal pain ($n=5$), headache ($n=6$), and dizziness ($n=2$). All 3 patients who received steroid treatment showed central obesity with cushinoid feature, however, other complications such as hyperglycemia, hypertension, or any psychological problem were not found. Any drug-related adverse effect \geq grade 3 was not reported in our patients.

3. Risk factors and clinical course of chronic ITP

The salient characteristics of patients with acute and chronic ITP are detailed in Table 1. Of the 64 patients in our study, 55 (85.9%) received a final diagnosis of acute ITP, while 9 patients (14.1%) eventually progressed to chronic ITP. Acute ITP was identified in our patients at a mean age of 34 ± 45 months, significantly younger than those ultimately diagnosed with chronic ITP at a mean age of 69 ± 37 months ($P=0.02$). The incidence of antecedent infection was significantly higher in patients with acute ITP compared to patients with chronic ITP (69.1% vs. 11.1%, $P<0.01$). Abrupt onset of symptoms was significantly more frequent in patients with acute ITP than in those who developed chronic

disease (92.3% vs. 44.4%, $P<0.01$). There was no significant difference in bleeding severity between patients with acute and chronic ITP. Notably, none of the 15 patients who presented without bleeding symptoms (incidentally diagnosed with ITP) developed chronic ITP. WBC count, % of lymphocytes, % of eosinophils, hemoglobin and platelet count at initial diagnosis showed no significant difference between patients acute ITP and those diagnosed with chronic ITP. Among 45 patients who received IVIG, those with platelet count $<45 \times 10^9/L$ at 1 month after IVIG showed significantly higher incidence of chronic ITP compared to those with platelet count $\geq 45 \times 10^9/L$ (88.8% vs. 44.4%, $P<0.01$).

The clinical course of the 9 chronic ITP patients is described in Table 2. All 9 of these patients presented with mild to moderate bleeding symptoms, while only 1 reported history of preceding infection. One month after initial IVIG treatment, median platelet count was $42 \times 10^9/L$ (range, $2 \times 10^9/L-88 \times 10^9/L$). At a median follow-up of 70 months, 3 patients still had platelet counts $<30 \times 10^9/L$ (i.e., NR), 4 patients maintained platelet counts of $30 \times 10^9/L-100 \times 10^9/L$ (PR), and 2 patients recovered to platelet counts $>100 \times 10^9/L$ (CR), measured at 23 and 38 months after initial diagnosis, respectively.

4. Clinical features of patients less than 100 days of age

The 17 patients less than 100 days of age at initial diagnosis

Table 1. Comparison of characteristics between patients with acute and chronic ITP

Characteristic	Acute ITP (n=55)	Chronic ITP (n=9)	P value
Age at diagnosis (mo)			0.02
Median (range)	13 (1-186)	71 (2-124)	
Mean \pm SD	34 \pm 45	69 \pm 37	
Sex			
Male:female	33 (60.0):22 (40.0)	5 (55.5):4 (44.4)	
Antecedent infection	38 (69.1)	1 (11.1)	<0.01
Recent vaccination	8 (14.5)	1 (11.1)	0.63
Abrupt onset	36/39 (92.3)	4/9 (44.4)	<0.01
Initial platelet count ($\times 10^9/L$)			
Median (range)	10 (0-84)	9 (1-58)	
Mean \pm SD	25 \pm 27	14 \pm 17	
Bleeding manifestation			0.10
No	15/54	0	
Mild	32/54	6	
Moderate	7/54	3	
Severe	0/54	0	
No. of patients with platelet count $\geq 45 \times 10^9/L$ *	32/36 (88.8)	4/9 (44.4)	<0.01

Values are presented as number (%) unless otherwise indicated. ITP, immune thrombocytopenia; SD, standard deviation.

*1 month after treatment.

Table 2. Clinical courses of patients with chronic ITP

UPN	Age (mo)	Initial presentation	Preceding infection	NOPHO score	Initial platelet count ($\times 10^9/L$)	Platelet count after 1st treatment ($\times 10^9/L$)	Subsequent treatment due to recurrent thrombocytopenia $< 20 \times 10^9/L$ (medication)	Recent platelet count ($\times 10^9/L$) (follow-up mo)
1	60	B	Yes	6	10	23	Yes (IVIg)	76 (+91)
2	71	P, E	No	4	9	88	Yes (IVIg)	95 (91)
3*	2	P	No	11	58	59	No	24 (+59)
4	124	B	No	4	3	28	Yes (IVIg)	208 (49)
5	76	P, E	No	11	4	2	Yes (IVIg, PD, DS, VCR)	8 (+49)
6	71	P, B, O	No	8	4	28	Yes (IVIg)	209 (124)
7	120	P, B	No	8	1	48	No	99 (76)
8	44	P, B	No	5	16	84	Yes (IVIg, PD, DS)	14 (+115)
9 [†]	55	B	No	9	24	42	Yes (IVIg)	45 (17)

UPN, unique patient number; ITP, immune thrombocytopenia; B, bruise; P, petechiae; E, epistaxis; O, oral mucosal bleeding; IVIg, intravenous immunoglobulin; PD, prednisolone; DS, dapsone; VCR, vincristine.

Nordic Society for Pediatric Haematology and Oncology (NOPHO) score: abrupt onset (5), age < 10 years (3), preceding infection (2), platelet count $< 5 \times 10^9/L$, wet purpura (1) and male gender (1).

*UPN 3 showed platelet count of $20 \times 10^9/L$ at 405 days after initial visit and received IVIg as initial treatment. [†]UPN 9 showed platelet count of $17 \times 10^9/L$ at 37 days after initial visit and received IVIg as initial treatment.

accounted for 26.6% of the patients in our study. All 17 were full-term babies, 11 male (64.7%) and 6 female patients (35.3%). Thirteen of these (76.5%) presented with petechiae and/or bruising, while the remaining 4 patients were diagnosed with ITP incidentally. Antecedent infection ($n=5$) and/or vaccination ($n=7$) within 2 weeks of diagnosis were noted in 8 patients (47.1%). However, all 17 patients < 100 days old had received one of the following vaccinations within a month prior to diagnosis: DTP (Diphtheria, Tetanus, and Pertussis), MMR (Measles, Mumps, and Rubella), polio, pneumococcus and/or rotavirus. At initial diagnosis, these 17 patients demonstrated median platelet count of $6 \times 10^9/L$ (range, $1 \times 10^9/L$ – $68 \times 10^9/L$). Five patients (29.4%) experienced spontaneous recovery to normal platelet count. Of the 12 patients (70.6%) who received IVIg, 11 (91.6%) achieved CR shortly after treatment; none of the patients developed recurrent thrombocytopenia. Only 1 of the patients < 100 days old (5.9%) was diagnosed with chronic ITP.

Discussion

ITP is a clinically heterogeneous bleeding disorder with a diverse natural history⁷. Indeed, although most patients recover, a minority of children with ongoing ITP develop severe, refractory disease^{4,5,8}. Moreover, the etiology of ITP the disease remains unclear, with several different mechanisms demonstrated as precipitating causes^{9–11}. Analogously, the acute and chronic forms of ITP have demonstrated differences in pathophysiology^{12,13}. Collectively, these complex clinical and pathophysiologic features produce a markedly heterogeneous population of children with ITP, with associated diagnostic and therapeutic challenges. Thus,

we tried to further investigate the clinical course of children diagnosed with ITP at our institution, following a policy of using IVIg as first-line therapy.

The Nordic Society for Pediatric Haematology and Oncology (NOPHO) ITP Working Group studied disease course in children with newly diagnosed ITP to propose a scoring system that utilized age at diagnosis, onset of symptoms, history of preceding infection, initial platelet count and gender to predict development of chronic ITP³. Concordantly, our study demonstrated significant association of older age, absence of antecedent infection and insidious onset of symptoms with the development of chronic ITP. However, initial platelet count and gender failed to demonstrate significant association with prediction of disease course in our patients.

Several other investigations have reported higher incidence of chronic ITP in patients > 10 years of age, as well as more favorable outcomes in those younger than 12 months^{5,8}. Yet, the clinical outcomes of ITP in infants < 100 days of age has not been exclusively analyzed. We specifically examined this underrepresented population, which comprised 26.6% of our total patient population. Among the distinctive findings in this cohort was its extremely high recovery rate of 94.1% (16 out of 17 patients), although there is limitation to draw firm conclusion due to low patient number. All of our patients < 100 days of age had received vaccinations within 1 month of diagnosis, possibly implicating vaccines as a potential trigger for developing ITP¹⁴. Yet considering the high rate of recovery of these patients in the early phases of ITP, age < 100 days, and recent vaccination warrant further investigation as potentially protective against development of chronic ITP.

Our study demonstrated an 85.9% incidence of acute ITP in our

patients, while the remaining 14.10% progressed to chronic ITP. Our observed incidence of acute ITP is slightly higher than that reported in prior investigations^{4,7,15,16}. The higher incidence of acute ITP in our study may be partially attributable to our relatively high proportion (40.7%) of patients <1 year of age, a population that has exhibited comparatively high rates of remission.

A recent comprehensive systematic review and meta-analysis by Heitink-Polle et al.¹⁷ assessing predictors of chronic ITP in children observed an apparent protective effect of IVIG treatment against the development of chronic disease. Thus, since all of our patients who required treatment for ITP (70.3% of our total patient population) received IVIG, our use of IVIG as first-line therapy might have influenced the course of ITP in our study, namely our high proportion of patients with final diagnosis of acute ITP. Additionally, we demonstrated that a final diagnosis of acute ITP was significantly more likely in patients with platelet counts $\geq 45 \times 10^9/L$ at 1 month after IVIG compared to patients with platelet counts $< 45 \times 10^9/L$ at 1 month after IVIG, suggesting that the degree of recovery in platelet counts following IVIG might represent a prognostic indicator for subsequent disease course. Other recent studies have reinforced the efficacy of IVIG in enhancing function of regulatory T cells (Treg) in various autoimmune disorders including ITP^{18,19}. Although its exact pharmacologic mechanism remains unclear, IVIG's stimulating effects on Tregs may restore the altered immunologic balance in autoimmune diseases and thereby influence the clinical course of disease. The action of IVIG in the modulation of Treg, and the consequent maintenance of immune tolerance, provides a rationale for therapeutic approach of ITP. Future studies are needed to find out if IVIG really protects against chronic ITP, if so, by what mechanisms this effect is caused, whether any of the impact of IVIG relates to increased clearance of infection or antibody load, and whether not treating results in persistent destruction of platelets influencing disease progression.

Dedicated treatment of acute ITP aims to prevent life-threatening bleeding complications, often initiated on the basis of platelet counts below a threshold level. In our study, we employed platelet counts $\leq 20 \times 10^9/L$ or signs of moderate to severe bleeding as indications for IVIG, obtaining initial response to therapy in 97.8% of treated children. On the other hand, approximately 86% of our patients with platelet count $> 20 \times 10^9/L$ experienced spontaneous recovery, suggesting that initial platelet counts above this threshold may indicate high probability of spontaneous recovery.

Perhaps the most serious complications of ITP are ICH, estimated to occur at a frequency of 0.19%–0.78%, predominantly in patients with platelet counts below $10 \times 10^9/L$ ²⁰. Notably, concurrent or recent head trauma has been reported in up to 25% of patients with ICH^{21,22}. Fortunately, none of our patients suffered severe bleeding, regardless of initial platelet count, though this may be partially attributable to our study's small patient pop-

ulation. The effects of immediate IVIG infusion could feasibly play a role in preventing severe bleeding. Currently, however, the initial therapy of children with acute ITP is controversial in regard to both indication and preferred therapeutic agent²³. In 2011, the American Society of Hematology recommended that "children with no bleeding or mild bleeding be managed with observation alone, regardless of platelet count"¹¹. Instead the authors of this study support guiding therapeutic management to most effectively minimize the impact of the disease on a patient's daily life, as well its associated anxiety in both patients and their parents. It should be noted that the diagnosis of ITP was established in our patients at a median age of 1 year, at which immature walking and running are accompanied by a relatively high incidence of trauma, thus further elevating bleeding risk. Finally, IVIG, the first-line treatment in our study, proved both safe and effective, with no significant adverse effects, and a response rate of approximately 98%. We therefore recommend that treatment decisions for ITP be individualized for each patient based on a combination of factors, including clinical signs, physical activity, platelet count as well as medical cost.

Our study has several limitations to consider, including the small patient population, which hinders the ability to draw firm conclusions. Secondly, due to retrospective nature of this study based on review of medical records, the quality of our data and its interpretation are dependent upon the quality of the original physician documentation. Finally, selection bias in treating patients with lower platelet counts and observing those with higher counts could have potentially influenced our analysis.

In conclusion, despite the substantial clinical variability in childhood ITP, the majority of patients follow a benign course of disease, regardless of initial platelet count, with approximately 86% of the patients in our study experiencing recovery within 1 year of initial diagnosis. Older age at diagnosis, absence of recent infection and insidious onset of symptoms were significantly associated with the development of chronic ITP in our patients. Additionally, platelet count $< 45 \times 10^9/L$ at 1 month after IVIG also demonstrated significant association with progression to chronic ITP, and could represent a valuable predictor of subsequent disease course. Finally, while the risk factors for developing chronic ITP are becoming increasingly clear, their potential impact on clinical practice requires further exploration, as does the influence of IVIG on the clinical course of ITP.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by the research grant of Chungbuk National University College of Medicine in 2014.

References

1. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190-207.
2. Lilleyman JS. Management of childhood idiopathic thrombocytopenic purpura. *Br J Haematol* 1999;105:871-5.
3. Edslev PW, Rosthoj S, Treutiger I, Rajantie J, Zeller B, Jonsson OG, et al. A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura in children. *Br J Haematol* 2007;138:513-6.
4. Roganovic J, Letica-Crepulja M. Idiopathic thrombocytopenic purpura: a 15-year natural history study at the Children's Hospital Rijeka, Croatia. *Pediatr Blood Cancer* 2006;47(5 Suppl):662-4.
5. ElAlfy M, Farid S, Abdel Maksoud A. Predictors of chronic idiopathic thrombocytopenic purpura. *Pediatr Blood Cancer* 2010;54:959-62.
6. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, 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.
7. Kühne T, Buchanan GR, Zimmerman S, Michaels LA, Kohan R, Berchtold W, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. *J Pediatr* 2003;143:605-8.
8. Donato H, Picon A, Martinez M, Rapetti MC, Rosso A, Gomez S, et al. Demographic data, natural history, and prognostic factors of idiopathic thrombocytopenic purpura in children: a multicentered study from Argentina. *Pediatr Blood Cancer* 2009;52:491-6.
9. Olsson B, Andersson PO, Jernas M, Jacobsson S, Carlsson B, Carlsson LM, et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat Med* 2003;9:1123-4.
10. Journeycake JM. Childhood immune thrombocytopenia: role of rituximab, recombinant thrombopoietin, and other new therapeutics. *Hematology Am Soc Hematol Educ Program* 2012;2012:444-9.
11. Toltl LJ, Arnold DM. Pathophysiology and management of chronic immune thrombocytopenia: focusing on what matters. *Br J Haematol* 2011;152:52-60.
12. Jernás M, Hou Y, Stromberg Celind F, Shao L, Nookaew I, Wang Q, et al. Differences in gene expression and cytokine levels between newly diagnosed and chronic pediatric ITP. *Blood* 2013;122:1789-92.
13. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. *Blood* 2009;113:6511-21.
14. Rinaldi M, Perricone C, Ortega-Hernandez OD, Perricone R, Shoenfeld Y. Immune thrombocytopenic purpura: an autoimmune cross-link between infections and vaccines. *Lupus* 2014;23:554-67.
15. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Pediatrics* 2008;121:e506-12.
16. Evim MS, Baytan B, Gunes AM. Childhood immune thrombocytopenia: long-term follow-up data evaluated by the criteria of the International Working Group on Immune Thrombocytopenic Purpura. *Turk J Haematol* 2014;31:32-9.
17. Heitink-Polle KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. *Blood* 2014;124:3295-307.
18. Ephrem A, Chamat S, Miquel C, Fisson S, Mouthon L, Caligiuri G, et al. Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis. *Blood* 2008;111:715-22.
19. Aslam R, Hu Y, Gebremeskel S, Segel GB, Speck ER, Guo L, et al. Thymic retention of CD4+CD25+FoxP3+ T regulatory cells is associated with their peripheral deficiency and thrombocytopenia in a murine model of immune thrombocytopenia. *Blood* 2012;120:2127-32.
20. Psaila B, Petrovic A, Page LK, Menell J, Schonholz M, Bussel JB. Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. *Blood* 2009;114:4777-83.
21. Lilleyman JS. Intracranial haemorrhage in idiopathic thrombocytopenic purpura. *Paediatric Haematology Forum of the British Society for Haematology. Arch Dis Child* 1994;71:251-3.
22. Bolton-Maggs P. Severe bleeding in idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003;25 Suppl 1:S47-51.
23. Cooper N. A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach? *Br J Haematol* 2014;165:756-67.