The Outcome of Immune thrombocytopenic purpura in childhood and the risk factors for chronicity

Baris Yilmaz[1], Ahmet Koc[2], Omer Dogru[2], Burcu Tufan Tas[1], emel senay[1], Nurşah Eker[2], and Gulnur Tokuc[2]

[1]Marmara University Training and Research Hospital
[2]Marmara University School of Medicine

October 5, 2020

Abstract

Abstract: Immune thrombocytopenic purpura (ITP) is an autoimmune disease presents with isolated thrombocytopenia (thrombocyte count < 100.000/mm3) and develops due to increased thrombocyte destruction by autoantibodies. ITP is the most common cause of pediatric thrombocytopenia. Usually a self-limiting disease with an acute course of 70% - 80%. However, 20% - 25% cases are chronical. These cases are follow-up and management difficult and expensive. It is important to distinguish events that may become chronic at the time of initial diagnosis. In this study, we sought clues to be able to choose, which the patient will be chronicle?

Abstract:

Immune thrombocytopenic purpura (ITP) is an autoimmune disease presents with isolated thrombocytopenia (thrombocyte count < 100.000/mm3) and develops due to increased thrombocyte destruction by autoantibodies. ITP is the most common cause of pediatric thrombocytopenia. Usually a self-limiting disease with an acute course of 70% - 80%. However, 20% - 25% cases are chronical. These cases are follow-up and management difficult and expensive. It is important to distinguish events that may become chronic at the time of initial diagnosis. In this study, we sought clues to be able to choose, which the patient will be chronicle?

Background: Immune thrombocytopenic purpura (ITP) is an autoimmune disease present with isolated thrombocytopenia and develops due to increased thrombocyte destruction by autoantibodies.(1, 2) ITP is the most common cause of pediatric thrombocytopenia. Usually a self-limiting disease with an acute course of 70% - 80%. However, 20-30% of cases become chronic. ITP most commonly seen between 2 and 5 years of age but occurs in all pediatric age groups. (2, 3)

In this study, we aimed to investigate the main characteristics (features) and outcomes of our pediatric ITP cases and whether there are any factors affecting chronicity.

Procedure: We analyzed retrospectively our 184 newly diagnosed pediatric ITP cases. In this study, a history of viral infections and vaccination, physical examination, laboratory findings, treatment modality, and efficacy in children under 18-years old with ITP were recorded. Thrombocytopenia persisting beyond 12 months was defined as "chronic ITP" whereas resolved thrombocytopenia within 12 months of diagnosis was defined as "acute ITP". The patients were divided into three age groups. Group 1 include the patients younger (smaller) than 2 years of age (57 patients), group 2 include the patients between 2 and 6 years of age (73 patients), and group 3 include the patients older (greater) than 6 years of age (54 patients). We evaluated the role of clinical and laboratory findings and treatment modalities in the chronicity of ITP.

As first-line treatment, 87 (47.3%) of patients were given Intravenous Immune Globulin (IVIG, 1 g/kg, 1 or 2 days), 65 (35.3%) were given methylprednisolone (20 mg/kg/day for three days, and 10 mg/kg/day for four days), and 32 (17.4%) of patients were followed without any medication.

Results: One hundred four patients were male (56.5%) and 80 (45.5%) were female. The mean age of patients was 5.4 ± 4.75 years at diagnosis. The most common bleeding site was skin in 83,7% of patients and none of the patients had central nervous system bleeding. In 92 patients (50%) no triggering cause could be identified. The most common triggering factor was upper respiratory tract infection (in 34,2 % of patients).

Thirty-nine patients (21.1%) who had persistent thrombocytopenia after 12 months of follow-up were accepted as chronic ITP. The ratio of acute/chronic ITP cases was 83/21 in males, and 62/18 in females (p=0.7). The treatment modality at first admission did not affect the development of chronic ITP (p=0.61). The most important factor in the development of chronic ITP was the age at diagnosis. The mean age at diagnosis was 4.54±4.18 years in acute ITP and 8.62±5.39 years in chronic ITP (p<0.0001) Acute and chronic ITP ratio were 53/4 for patients less than 2 years of age, 60/13 for patients between 2 and 6 years of age, and 31/23 for over than 6 years of age (p<0.0001). The thrombocyte counts and mean platelet volume (MPV) at diagnosis did not affect chronicity. Total leukocyte count at diagnosis had also no effect on chronicity, but mean absolute neutrophil count (ANC) was significantly higher (p=0.007) and mean absolute lymphocyte count (ALC) was significantly lower (p<0.0001) in chronic ITP patients. But when these findings were re-evaluated according to each age group, we did not find any important differences between acute and chronic cases for mean ANC and ALC, except ALC levels had only a small effect on the 2nd (2-6 years) group (p:0.048).

Conclusions: Although ITP has a good prognosis in most of the patient in childhood, it may become chronic in about 20 % of patients. Our results support that, high age most important factor for ITP's chronicity. Infantile ITP prognosis better than older children, and watch-and-wait strategy could be a safe treatment choice.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disease present with isolated thrombocytopenia (thrombocyte count < 100.000/mm3), develops due to increased thrombocyte destruction by autoantibodies, and its mostly benign, and self-limited disease. (1) The peak incidence is seen between two and 5-years of age and in 60%-80% of patients, it resolves with remission within 12 months. (2)

The incidence of ITP was reported as 7.2-9.5/100.000 per year in North America, whereas European studies reported the incidence as 2.9-5.3/100.000. (2, 4) To avoid terminological conflict in definition, the first 3 months of diagnosis is defined as "newly diagnosed ITP", three to 12 months of disease is defined as "persistent ITP" and the disease persist over 12 months of duration is defined as "chronic ITP".(5)

ITP pathophysiology is a very complex condition. The accused factors in ITP pathogenesis are Ab-mediated (etc. against to GPIIb-GPIIIa, GPIb-GPIX) destruction, impaired megakaryopoiesis (Ab and/or cellular destruction, slightly elevated TPO), elevated Tcell activity.(2) These Ab's can be oligoclonal or polyclonal, and different subclass IgG families. (6)

Corticosteroids and intravenous immunoglobulin (IVIG), anti Rh D immune globulin (only Rh-positive patients) are commonly used in the treatment of ITP in children as first-line treatment options.(7-9)

The second line treatment options are anti-Rhesus-D immunoglobulin, immunosuppressive agents (azathioprine, cyclosporine, sirolimus, mycophenolate mofetil), anti-CD20 (rituximab), and several chemotherapeutics (iphosphamide, vinca alkaloids) or combinations of these options.(10, 11) Recently refractory cases are treated with thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag) and they are licensed in the treatment of ITP. (12-14)

Chronicity factors for pediatric ITP; advanced age, insidious beginning, highly (especially > 20.000/mm^3) platelet numbers, and female gender.(15)

In this study, we aimed to determine the main characteristics and outcomes of our pediatric ITP cases and whether there are any risk factors affecting chronicity.

MATERIAL AND METHOD

In this retrospective study, we analyzed 184 children between 3 months to 18 years of age who had newly diagnosed ITP, in Marmara University Training and Research Hospital, Pediatric Hematology Unit, between 01.01.2012 and 12.31.2017.

Data including patient and disease characteristics such as age, sex, presenting symptoms at the initial diagnosis, and findings in physical examination, treatment modality, and outcome were collected in standard forms for each patient. Hematologic data including initial complete blood count, analysis of peripheral blood smears, and bone marrow aspiration slides were all noted.

ITP was diagnosed in a child when platelet count under 100.000/μL with normal hemoglobin and white blood cell count and there is no other clinical and laboratory abnormality.

Only the patients who had platelet counts under 50.000/μL were admitted to this study because most children with platelets count between 50,000 and 100,000/μL do not apply to the hospital or do not need treatment. The patients who had other causes of thrombocytopenia (bone marrow failure, malignancy, primary thrombocytopenia's, infections, etc.), maternal ITP, and patients without regular follow-up are excluded from the study.

The patients were treated if they had a platelet count lower than 10.000/μL, or if they had wide-spread petechia, purpura, or bleeding symptoms.

As first-line treatment, 87 (47.3%)of patients were given Intravenous Immune Globulin (IVIG, 1 g/kg, 1 or 2 days), 65 (35.3%) were given methylprednisolone (20 mg/kg/day for three days, and 10 mg/kg/day for four days), and 32 (17.4%) of patients were followed without any medication.

In children who were given methylprednisolone treatment (MP), bone marrow aspirations were done before starting treatment with MP. Although bone marrow examination is not recommended for every patient in current ITP guides, bone marrow examination was performed before treatment in patients who will take steroids due to routine application in our hospital during the study period.

Thrombocytopenia persisting beyond 12 months was defined as "chronic ITP" whereas resolved thrombocytopenia within 12 months of diagnosis was defined as ''acute ITP". The patients were divided into three age groups. Group I include the patients younger (smaller) than 2 years of age (57 patients), group 2 include the patients between 2 and 6 years of age (73 patients), and group 3 include the patients older (greater) than 6 years of age (54 patients).

The data of patients were analyzed using the IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). The data were expressed as mean ± standard deviation (SD). The Shapiro–Wilk and Kolmogorov-Simirnov tests were used for normality analysis of the data. If the skewness and kurtosis range between to -1,5 and +1,5, we accepted the data was normality. The unpaired Student t-test was used for comparison of normal parameters of acute and chronic ITP patients at diagnosis. Mann-Whitney U test was used for comparison of non-normal differenced parameters of acute and chronic ITP patients at diagnosis. The unpaired Student t-test was used for comparison of mean age, mean hemoglobin level, mean platelet count, mean total leukocyte count, mean absolute neutrophil count (ANC), and mean absolute lymphocyte count (ALC) of acute and chronic ITP patients at diagnosis. Intergroup rate comparisons were performed with Pearson chi-square and Fisher's exact tests.

The confidence level of 95% and p values of < 0.05 were considered as statistically significant.

RESULTS

One hundred-four of patients were male (56.5%) and 80 (45.5%) were female. The mean age of patients was 5.4 ± 4.75 years at diagnosis. All patients divided three study groups. Group 1: 0-2 years, group 2: 2,01-6

years, and group 3: 6,01-18 years. (Table 1)

The most common bleeding site was skin in 83,7%, followed by mucosal bleedings in 9 .7% of patients. Ten patients (5.4%) had no bleeding symptom and thrombocytopenia were detected when complete blood count has done due to other causes. None of the patients had a life-threatening condition such as central nervous system bleeding. Mean hemoglobin levels, total leukocyte count, absolute neutrophil count, absolute lymphocyte count, platelet count, and MPV levels were calculated and evaluated between three groups. (summarized Table 2)

No triggering cause could be identified in 92 (50%) of patients. The most common triggering factor was upper respiratory tract infection in 63 (34,2 %) of patients. Six (3.3%) patients had varicella and five (2.7%) patients had lower respiratory tract infections before the diagnosis of ITP. At the serologic tests, EBV VCA IgM was positive in four (2.2%) cases, CMV IgM was positive in two cases (1.1%) and rubella IgM was positive in two cases (1.1%). Three patients had a history of preceding rotavirus vaccination.

When patients evaluated according to first-line treatment options, 87 (47.3%) of patients were given IVIG, 65 (35.3%) patients were given methylprednisolone, and 32 (17.4%) patients were followed without any medication. Third and later treatment strategies were low dose-long term prednisolone treatment 10 (5.4%) patients, eltrombopag 7 (3.8%) patients, rituximab treatment five (2.7%) patients, splenectomy five (2.7%) patients, and mycophenolate mofetil two (1.1%) patients.

We saw a high level of difference between the age groups in the choice of treatment options. ($p<0.0001$) IVIg treatment option was used by especially in the infancy age group. (Table 1 and 3) The treatment modality at first admission was found to not affect the progression of chronic ITP ($p=0.61$). Besides, when we examined according to age groups, we did not observe any effect of the first choice of treatment in acute ITP patients on chronicity. (group 1 p: 0.4, group 2 p: 0.42, group 3 p: 0.33)

Some characteristics of the patient according to treatment modality were given in Table 1.

Thirty-nine patients (21.1%) who had persistent thrombocytopenia after 12 months of follow-up were accepted as chronic ITP.

The ratios of chronicity were 20.19% in males (21 in 104 patients) and 22.5% in females (18 in 80 patients). There was no difference between the genders in terms of chronicity in our patients (p: 0.7), and there was no difference between the genders when examined in the age groups.

The most important factor in the development of chronic ITP was the age at the initial diagnosis. The mean age at diagnosis was 4.54 ± 4.18 years in acute ITP and 8.62 ± 5.39 years in chronic ITP ($p<0.0001$). Acute and chronic ITP ratio was 53/4 for the patients younger than 2 years of age, 60/13 for the patients between 2 and 6 years of age, and 31/23 for over 6 years of age ($p<0.0001$). Also, we evaluated by the age groups; and we found statically significant high-level differences between three age groups. (p: 0.002) The rate of second-line treatment requirement and chronicity ratio according to age groups and treatment methods are given in Table 4.

The thrombocyte counts and mean platelet volume (MPV) at diagnosis did not affect chronicity in all patients. Besides, these values similar to all the age groups, and no differences between three age groups.

The thrombocyte counts and mean platelet volume (MPV) at diagnosis did not affect chronicity. Total leukocyte count at diagnosis had also no effect on chronicity, but mean absolute neutrophil count (ANC) was significantly higher ($p=0.007$) and mean absolute lymphocyte count (ALC) was significantly lower ($p<0.0001$) in chronic ITP patients. However, when these findings were re-evaluated by the age groups, it was concluded that the differences occurred based on ages. But when these findings were re-evaluated according to each age group, we did not find any important differences between acute and chronic cases for mean ANC and ALC, except only ALC levels were slightly lower in the chronic group in the 2^{nd} age (2-6 years) group (p:0.031).

Mean hemoglobin levels, total leukocyte count, absolute neutrophil count, absolute lymphocyte count, platelet count, and MPV according to age groups and treatment methods are given in Table 2.

We did not see any effect on the chronicization of a cause such as infection or vaccination before acute ITP. Splenectomy was performed in five (2.7%) of chronic ITP patients.

DISCUSSION

About 20-30% of childhood ITP progresses to chronic ITP. (2, 16, 17) It is important to predict which factors are important in the progression of chronicity. Although it is difficult to assume which patient will develop chronic ITP, in a systematic review and meta-analysis by Heting-Pollé et al. advanced age at diagnosis, insidious onset disease, absence of a history of infection preceding, high thrombocyte count at diagnosis, female gender had been reported as risk factors of chronicity in childhood ITP. (16) Deel et al. had evaluated 204 children with a diagnosis of ITP. They also reported that progression to chronicity was significantly increased in children above 8 years of age ($p<0.001$). (18) We also found that the risk of progression of chronicity was statistically significant. On the other hand, infantile ITP patients are different than other age groups ITP patients. Farhangi et al. examined 187 children under 2 years of age diagnosed with ITP. They observed that patients ITP diagnosed under 3 months had more chronicity than patients aged 3-24 months. (19)

insidious onset disease,

We did not see any effect of infections or vaccinations before acute ITP on the chronicity (p: 0.2)

In Deel et al. study (18) they reported that ALC at diagnosis showed no difference in chronic and acute ITP groups, however, at third, 6th, 9th and 12th months of diagnosis ALC counts were found to be significantly lower in the chronic group. In our study, ALC at diagnosis was lower in the chronic ITP group at diagnosis and this difference was statistically significant ($p<0.0001$). Our study has also shown that mean ANC was higher in patients with chronic ITP than patients who resolved in the first 12 months ($p= 0.036$), while there were no important differences between the two groups according to mean platelet counts ($p=0.839$).

Akbayram et al. studied possible predictors of chronicity in childhood ITP and found that sex did not affect the progression of chronicity in childhood ITP. In this study, we also found that there was no important difference in the chronicity rate between males and females (20.19% vs 22.5%) patients ($p=0.7$). (20)

Although there are some studies, which support the superiority of IVIG on, corticosteroids as initial therapy, there are studies, which showed that initial therapy preference, makes no change on the progression of chronicity.(21, 22)

Akbayram et al. evaluated the effect of initial therapy on the progression of chronicity and reported no difference between high dose steroids, low dose steroids, and IVIG therapy groups.(20) In our study; either high dose methylprednisolone or IVIG was initiated as first-line therapy. We also found no difference in the progression of chronicity between HDMP and IVIG groups. Baronci et al. evaluated the treatment response duration of treatment choice with high dose Methylprednisolone (MP), low dose MP, IVIG, and high dose dexamethasone selection, with the fastest response with high dose MP and IVIG. (23)

An alternate to therapy is "watchful waiting" for ITP if the thrombocyte count is $> 20.000/mm3$. Besides thrombocyte count, "bleeding score" is important in the decision of treatment options. (24)

Rituximab may be considered in chronic cases with bleeding, however, splenectomy seems to be more efficient.(25-27) Interesting an alternative therapy for chronic, pediatric ITP patients is a Japanese medicine drug called cepharanthin. It is a bisbenzylisoquinoline (biscolaurine) alkaloid group wide-ranged effective immunosuppressive drug.(28) Yamazaki et al. were use this drug on 46 chronic-resistant, <16 years Japanese ITP patients.(29) In this study shown cepharantine has used a safe and effective alternative corticosteroid-sparing drug.

Currently, in refractory cases, successful results have been reported for TPO receptor agonist, romiplostim (30) and eltrombopag (31, 32) as a second-line therapy option. In two splenectomized and five non-splenectomized chronic ITP cases, we achieved a complete response to eltrombopag therapy at a dose of 25-75mg/day PO.

CONCLUSIONS

Prediction of chronic and refractory cases at diagnosis will be helpful to achieve higher treatment success. We conclude that higher patient age, lower ALC at initial diagnosis may have some negative effect on chronicity, while gender, the severity of symptoms, presence of infection history, platelet count and MPV at diagnosis and first-line treatment modality does not have any important effect.

The authors declare no conflict of interest. There was no financial support from any person or institution for this study.

References

1. Rehman A. Acute immune thrombocytopenic purpura in children. Turk J Hematol. 2007;24:41-51.

2. Bussel JB MC. Lanzkowsky's Manual of Pediatric Hematology and Oncology 6th ed. ed: Elsevier; 2016.

3. Sandoval C, Visintainer P, Ozkaynak MF, Tugal O, Jayabose S. Clinical features and treatment outcomes of 79 infants with immune thrombocytopenic purpura. Pediatric blood & cancer. 2004;42(1):109-12.

4. Masamune Higashigawa TM, Ayako Yoshino, Kazuyuki Matsuda, Mitsue Ito, Tomoaki Maji and Ryouji Ichimi. Incidence of childhood primary immune thrombocytopenic purpura. Pediatrics International 2015;57:1041–3. doi: doi: 10.1111/ped.12788.

5. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11):2386-93. Epub 2008/11/14. doi: 10.1182/blood-2008-07-162503. PubMed PMID: 19005182.

6. Chan H, Moore JC, Finch CN, Warkentin TE, Kelton JG. The IgG subclasses of platelet-associated autoantibodies directed against platelet glycoproteins IIb/IIIa in patients with idiopathic thrombocytopenic purpura. British journal of haematology. 2003;122(5):818-24.

7. Bolton-Maggs P. Idiopathic thrombocytopenic purpura. Archives of disease in childhood. 2000;83(3):220-2.

8. Beck CE, Nathan PC, Parkin PC, Blanchette VS, Macarthur C. Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: a systematic review and meta-analysis of randomized controlled trials. J Pediatr. 2005;147(4):521-7. Epub 2005/10/18. doi: 10.1016/j.jpeds.2005.04.032. PubMed PMID: 16227040.

9. Bansal D, Bhamare TA, Trehan A, Ahluwalia J, Varma N, Marwaha RK. Outcome of chronic idiopathic thrombocytopenic purpura in children. Pediatr Blood Cancer. 2010;54(3):403-7. Epub 2009/11/13. doi: 10.1002/pbc.22346. PubMed PMID: 19908301.

10. D'Orazio JA, Neely J, Farhoudi N. ITP in children: pathophysiology and current treatment approaches. Journal of pediatric hematology/oncology. 2013;35(1):1-13.

11. Kuhne T. Advances in chemical pharmacotherapy for the treatment of pediatric immune thrombocytopenia. Expert Opinion on Pharmacotherapy. 2018;19(7):667-76. doi: 10.1080/14656566.2018.1458091.

12. Kuhne T. Treatment of pediatric primary immune thrombocytopenia with thrombopoietin receptor agonists. Semin Hematol. 2015;52(1):25-30. Epub 2015/01/13. doi: 10.1053/j.seminhematol.2014.10.004. PubMed PMID: 25578416.

13. Ehrlich LA, Kwitkowski VE, Reaman G, Ko CW, Nie L, Pazdur R, Farrell AT. US Food and Drug Administration approval summary: Eltrombopag for the treatment of pediatric patients with chronic immune (idiopathic) thrombocytopenia. Pediatric blood & cancer. 2017;64(12):e26657.

14. Neunert C, Despotovic J, Haley K, Lambert MP, Nottage K, Shimano K, Bennett C, Klaassen R, Stine K, Thompson A. Thrombopoietin receptor agonist use in children: data from the pediatric ITP consortium of North America ICON2 Study. Pediatric blood & cancer. 2016;63(8):1407-13.

15. Lee MS, Kim WC. Intracranial hemorrhage associated with idiopathic thrombocytopenic purpura: report of seven patients and a meta-analysis. Neurology. 1998;50(4):1160-3. Epub 1998/05/05. doi: 10.1212/wnl.50.4.1160. PubMed PMID: 9566417.

16. 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(22):3295-307. Epub 2014/10/12. doi: 10.1182/blood-2014-04-570127. PubMed PMID: 25305206.

17. Kuhne T, Imbach P, Bolton-Maggs PH, Berchtold W, Blanchette V, Buchanan GR, Group ICIS. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. The lancet. 2001;358(9299):2122-5.

18. Deel MD, Kong M, Cross KP, Bertolone SJ. Absolute lymphocyte counts as prognostic indicators for immune thrombocytopenia outcomes in children. Pediatr Blood Cancer. 2013;60(12):1967-74. Epub 2013/09/17. doi: 10.1002/pbc.24628. PubMed PMID: 24038723.

19. Farhangi H, Ghasemi A, Banihashem A, Badiei Z, Jarahi L, Eslami G, Langaee T. Clinical Features and Treatment Outcomes of Primary Immune Thrombocytopenic Purpura in Hospitalized Children Under 2-Years Old. Iranian journal of pediatric hematology and oncology. 2016;6(1):24.

20. Akbayram S, Dogan M, Ustyol L, Akgun C, Peker E, Bilici S, Caksen H, Oner AF. The clinical outcome of 260 pediatric ITP patients in one center. Clin Appl Thromb Hemost. 2011;17(6):E30-5. Epub 2010/08/18. doi: 10.1177/1076029610379849. PubMed PMID: 20713486.

21. Tamminga R, Berchtold W, Bruin M, Buchanan GR, Kuhne T. Possible lower rate of chronic ITP after IVIG for acute childhood ITP an analysis from registry I of the Intercontinental Cooperative ITP Study Group (ICIS). Br J Haematol. 2009;146(2):180-4. Epub 2009/05/27. doi: 10.1111/j.1365-2141.2009.07743.x. PubMed PMID: 19466971.

22. Yacobovich J, Revel-Vilk S, Tamary H. Childhood immune thrombocytopenia–who will spontaneously recover? Semin Hematol. 2013;50 Suppl 1:S71-4. Epub 2013/05/17. doi: 10.1053/j.seminhematol.2013.03.013. PubMed PMID: 23664522.

23. Baronci C, Pansini V, Funaro D, Coletti V, Caruso R, Rossi GD. Idiopathic thrombocytopenic purpura (ITP) in children. Pediatric blood & cancer. 2006;47(S5):665-7.

24. 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(23):4777-83. Epub 2009/09/22. doi: 10.1182/blood-2009-04-215525. PubMed PMID: 19767509; PMCID: PMC2786288.

25. Sabhan AH, Al-Jadiry MF, Ghali HH, Abed WM, Al-Hadad SA. Chronic immune thrombocytopenic purpura in children overview of 60 patients. Pediatric Hematology Oncology Journal. 2016;1(1):9-12.

26. Oved JH, Lee CS, Bussel JB. Treatment of children with persistent and chronic idiopathic thrombocytopenic purpura: 4 infusions of rituximab and three 4-day cycles of dexamethasone. The Journal of pediatrics. 2017;191:225-31.

27. Liang Y, Zhang L, Gao J, Hu D, Ai Y. Rituximab for children with immune thrombocytopenia: a systematic review. PLoS One. 2012;7(5):e36698. Epub 2012/06/06. doi: 10.1371/journal.pone.0036698. PubMed PMID: 22666325; PMCID: PMC3364261.

28. Sato T, Morita I, Fujita H, Ono M, Kimishima A, Tomiyama J, Murota S. Pharmacological characterization of cepharanthin in chronic idiopathic thrombocytopenic purpura. Platelets. 2001;12(3):156-62. Epub 2001/04/17. doi: 10.1080/09537100120039334. PubMed PMID: 11304417.

29. Yamazaki T, Shibuya A, Ishii S, Miura N, Ohtake A, Sasaki N, Araki R, Ota Y, Fujiwara M, Miyajima Y. High-dose Cepharanthin for pediatric chronic immune thrombocytopenia in Japan. Pediatrics International. 2017;59(3):303-8.

30. Tarantino MD, Bussel JB, Blanchette VS, Despotovic J, Bennett C, Raj A, Williams B, Beam D, Morales J, Rose MJ, Carpenter N, Nie K, Eisen M. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016;388(10039):45-54. Epub 2016/04/23. doi: 10.1016/s0140-6736(16)00279-8. PubMed PMID: 27103127.

31. Bussel JB, de Miguel PG, Despotovic JM, Grainger JD, Sevilla J, Blanchette VS, Krishnamurti L, Connor P, David M, Boayue KB. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. The Lancet Haematology. 2015;2(8):e315-e25.

32. Grainger JD, Locatelli F, Chotsampancharoen T, Donyush E, Pongtanakul B, Komvilaisak P, Sosothikul D, Drelichman G, Sirachainan N, Holzhauer S. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. The Lancet. 2015;386(10004):1649-58.

Hosted file

`ITP-TABLES.pdf` available at https://authorea.com/users/327768/articles/484552-the-outcome-of-immune-thrombocytopenic-purpura-in-childhood-and-the-risk-factors-for-chronicity