



Advances in management of pediatric chronic immune thrombocytopenia: a narrative review

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Immune thrombocytopenia (ITP) is a disease in which thrombocytopenia occurs because of immune-mediated platelet destruction and decreased platelet production. Although many pediatric patients with ITP experience spontaneous remission or reach remission within 12 months of first-line therapy, approximately 20% progress to chronic ITP. Patients who do not respond to first-line treatment or experience frequent relapses are of great concern to physicians. This review summarizes recent treatments for second-line treatment of pediatric chronic ITP.

Keywords: Dapsone; Idiopathic thrombocytopenic purpura; Rituximab; Splenectomy; Thrombopoietin

Introduction

Immune thrombocytopenia (ITP) is a disease in which thrombocytopenia occurs because of immune-mediated platelet destruction and decreased platelet production. The overall pediatric ITP incidence in Korea is 18.1 per 100,000 person-years [1].

The generation of antiplatelet autoantibodies is thought to be a fundamental event in ITP, although the pathophysiology of this condition is not fully understood [2]. Through the activation of Fc receptors, these autoantibodies target platelets for destruction by macrophages in the spleen, liver, or both. Spleen tyrosine kinase regulates this process. The ability of megakaryocytes to produce platelets may be inhibited by the autoantibodies, which can kill platelets in other ways. Major histocompatibility complex class II delivers antigens from phagocytosed platelets to T-cell receptors, activating autoreactive T cells. T helper (Th) cells in ITP are skewed toward type 1 (Th1) and type 17 (Th17) phenotypes, and

regulatory T cell activity is decreased. These T-cell alterations are thought to be pathologic.

Bleeding that requires treatment occurs in 30% to 56% of patients with newly diagnosed pediatric ITP [3-5], and bleeding that requires immediate management is reported in up to 4% of all patients with ITP. Fatal intracranial hemorrhage is reported in up to 3% of all patients with ITP [6-13]. It is known that approximately 2/3 of adult ITP cases progress to chronic ITP, but 20% to 25% of pediatric ITP cases persist to chronic ITP [14]. This review summarizes recent treatments for pediatric chronic ITP.

Definition of chronic immune thrombocytopenia

According to the definition of an international working group, ITP is categorized as newly diagnosed, persistent, or chronic according to disease duration. Newly diagnosed ITP is diagnosed within 3

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months of onset, persistent ITP has lasted between 3 and 12 months, and chronic ITP is defined as ITP lasting more than 12 months [15].

Natural course of immune thrombocytopenia

Three percent to 10% of cases are children with one or more comorbidities, and ITP in children is often acute and resolves spontaneously [16,17]. According to data from the Pediatric and Adult Registry on Chronic ITP, 70% of patients had spontaneous remission within 6 months, and the mean age of patients with late remission at 12 and 24 months was higher than that of children with early remission at 6 months. Twenty-eight percent of pediatric patients with chronic ITP achieved remission within 24 months.

ITP often has a benign course in pediatric patients, and 86% of these patients fully recover within 1 year of diagnosis. After extensive follow-up, children with chronic ITP display a high rate of remission [18].

At 2 and 5 years after diagnosis, the chances of complete remission of chronic ITP were 50% and 76%, respectively [19]. Three to 4 years after diagnosis, approximately 45% of children with chronic ITP spontaneously improve, while 2/3 of patients continue to have a platelet count below $50 \times 10^9/L$ [20].

Diagnostic approach for patients with chronic immune thrombocytopenia

Bone marrow aspiration and biopsy are not required in children with newly diagnosed ITP who show isolated thrombocytopenia on complete blood count and no abnormalities other than evidence of thrombocytopenia on blood smear or physical examination. Bone marrow examination is not necessary, even when considering second-line therapy [21,22]. According to the recent American Society of Hematology (ASH) guidelines, if spontaneous platelet increase is not observed for 3 to 6 months or more or does not respond to treatment, bone marrow aspiration, biopsy, and cytogenetics should be performed. Next-generation sequencing or targeted sequencing should be considered [23]. Tests for autoimmune diseases such as lupus (antinuclear antibody, anticardiolipin antibody, and lupus anticoagulant) that require immunosuppressive treatment and tests for chronic infections caused by, for example, hepatitis virus, cytomegalovirus, human immunodeficiency virus, and *Helicobacter pylori* are also required.

Management of chronic immune thrombocytopenia

1. Thrombopoietin receptor agonists

Thrombopoietin is a major factor that regulates megakaryocyte production. The main mechanism of action of thrombopoietin receptor agonists (TPO-RAs) is to stimulate bone marrow megakaryocytes [24,25]. Eltrombopag and romiplostim are TPO-RA drugs approved by the U.S. Food and Drug Administration for use in children. Both drugs showed efficacy and safety compared with placebo in children, but no clinical trials comparing the two drugs have been conducted. The ASH 2019 guidelines recommend the use of TPO-RA rather than rituximab in children with ITP who do not respond to first-line treatment [26].

2. Eltrombopag

Eltrombopag is a once-daily, oral TPO-RA requiring some dietary restrictions. Peak levels are obtained 2 to 6 hours after oral ingestion. After a single oral dose of 75 mg, the bioavailability was > 52%. When taking eltrombopag with a high-fat, high-calcium diet versus on an empty stomach, the area under the curve decreased by 59%, the maximum serum concentration (C_{max}) decreased by 65%, and the time to reach C_{max} was delayed by 1 hour [27]. Additionally, eltrombopag is metabolized in the liver, and its half-life ranges from 21 to 32 hours [28]. The dose of eltrombopag depends on the patient's age, ethnicity, and hepatic function. In addition, the dose should be adjusted according to platelet response (maximum dose, 75 mg/day).

The efficacy and safety of eltrombopag in children were verified in two multicenter randomized trials, PETIT and PETIT2 [29,30]. Eltrombopag showed response rates of 62% in PETIT and 75% in PETIT2. It also showed a reduction in bleeding events and the requirement for additional treatments. The median time to response was 12 to 20 days depending on the patient's age.

In a recent retrospective multicenter study conducted in 17 centers affiliated with the Italian Association of Pediatric Hematology and Oncology, 68% and 44% of patients achieved platelet counts of $30 \times 10^9/L$ and $100 \times 10^9/L$, respectively [31].

3. Romiplostim

In a phase 1/2 trial with children, romiplostim showed an improvement in platelet counts compared with that of placebo [32]. In that study, 88% of patients in the romiplostim group had platelet counts $\geq 50 \times 10^9/L$ and $20 \times 10^9/L$ above baseline for 2 consecutive weeks. In contrast, none of the patients in the placebo group showed improvement. In the open label extension study after the

phase 1/2 trial, the median average weekly dose was 5.4 µg/kg [33]. In a phase 3 trial, romiplostim showed a high rate of platelet response and reduced rate of bleeding events in pediatric patients with chronic ITP [34]. A durable platelet response was achieved in 52% of patients in the romiplostim group compared with 10% in the placebo group.

The starting dose is 1 µg/kg/week and is increased by 1 µg/kg/week according to the platelet count to a maximum of 10 µg/kg/week. The goal is to determine the minimum dose that maintains a platelet count of at least 50×10^9 /L. If there is no response after 4 weeks of maximum weekly dosing, other treatments should be considered.

Unlike eltrombopag, romiplostim is not affected by diet. It is known that the serum concentration of the drug is the same in adults and in children over 1 year of age. Platelet production peaks on days 8 to 15 after romiplostim injection and returns to baseline on days 22 to 28 [35]. In an adult study, 32% of patients maintained a platelet count of $> 50 \times 10^9$ /L after discontinuing romiplostim following 12 months of treatment [36]. Romiplostim was also effective in patients with an ITP duration of ≤ 1 year who failed first-line treatment [37]. In the pediatric study, there were no treatment-related serious adverse events. Headache and epistaxis are the most common side effects in both pediatric and adult patients [32-34]. Bone marrow examination was not routinely performed in pediatric studies despite the controversial issue of bone marrow fibrosis in adults. However, no bone marrow reticulin or fibrosis was observed in five bone marrow biopsies performed in the pediatric extension study [33].

4. Rituximab

Rituximab is a monoclonal antibody against CD20+ B cells that produce autoantibodies to platelets [38]. Rituximab is infused at 375 mg/m² once weekly over 4 weeks [39-42]. Rituximab produced a complete response in 22% to 79% of pediatric patients with ITP. The 58% of patients who responded to rituximab maintained platelet counts of $> 50 \times 10^9$ /L for at least 1 year after rituximab treatment, and 25% to 30% maintained a response for more than 5 years. Most patient relapse occurred within 2 years [43,44]. Rituximab, when administered in combination with dexamethasone in adults, showed superior effects compared to dexamethasone alone [45-47]. In a study in which rituximab and dexamethasone were combined in children, 30% of patients showed prolonged remission after treatment with a standard dose of rituximab and 4 days of dexamethasone [48]. Reported toxicities of rituximab, including neutropenia, infection, hypogammaglobulinemia, and infusion-related reactions, were minimized with steroid pre-medication.

5. Dapsone

Dapsone is an inexpensive and effective therapeutic option for the treatment of chronic ITP. Since it was first known to be effective against chronic ITP in 1988, dapsone has been one of the oldest and safest agents in the management of chronic ITP [49]. The mechanism of action of dapsone is not well understood. Hemolysis caused by dapsone is known to interfere with platelet destruction in the reticuloendothelial system and suppress antiplatelet antibodies.

Dapsone has a response rate of 50% to 72%, a complete response of 20% to 48%, and a partial response of 17% to 48% [50-52]. The duration to response is approximately 1 to 3 months, and the relapse rate is approximately 10% to 20%. As well-known hematologic adverse effects, methemoglobinemia and hemolysis occur in 10% to 20% of cases. Rarely, agranulocytosis and aplastic anemia may also occur, and characteristic hypersensitivity reactions such as fever, eosinophilia, and skin rash may occur with dapsone [50-52].

There are few reports on the use of dapsone in children. However, because it is a drug whose safety has been verified for a long time, it is worth considering as an alternative if the disease is refractory to other treatments.

6. Splenectomy

Splenectomy is an effective therapeutic option for children with chronic ITP. Recently, TPO-RAs and rituximab have been preferred, and splenectomy is performed less frequently today. Owing to the development of new treatments, approximately 90% of patients now show complete remission, and less than 5% of patients show refractoriness.

The splenectomy registry of the Intercontinental Cooperative ITP Study Group collected the splenectomy data of pediatric patients with ITP. The overall response rate was 93%, and 81% of patients showed complete response. Of the latter patients, 76% showed a sustained complete response and 24% showed fluctuation of platelet counts to $< 100 \times 10^9$ /L [53].

Although there is a low risk of perioperative adverse events, the long-term outcomes and quality of life should be considered. Fatal sepsis and lifelong susceptibility to bacterial infection are of concern. The incidence of sepsis and venous thromboembolism in adults with ITP is approximately 10%, and age and comorbidities are important factors [54]. Prognostic factors that can be expected for remission after splenectomy are older patient age and good response to intravenous immunoglobulin and steroids in children [53,55-59].

Conclusion

The clinical course and treatment of chronic ITP were reviewed. Due to the recent introduction of TPO-RAs in the treatment of pediatric chronic ITP, the health-related quality of life of pediatric patients with chronic ITP has improved compared to that of patients receiving conventional treatment [60–62]. However, further studies on the treatment effects of drugs and prognostic factors should be conducted. Pediatric chronic ITP treatment should be individualized and based on the risks and benefits of treatment.

Notes

Conflicts of interest

Jae Min Lee has been an editorial board member of *Journal of Yeungnam Medical Science* since 2021. He was not involved in the review process of this manuscript. There is no conflicts of interest to declare.

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