

Management and Treatment of Primary Immune Thrombocytopenia in Children

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Abstract Primary immune thrombocytopenic purpura (ITP), the most common isolated thrombocytopenia of childhood, is involved in immunological mechanisms. ITP has shown heterogeneous pathophysiology, clinical features, and response to treatment. Most children with primary ITP recover within 6–12 months, but some patients who develop refractory or chronic ITP require especially careful medical management. To date, most conventional treatments consist of immunosuppressive or immune-modulating drugs. The International Consensus Report on the management of primary ITP has stated the goal for ITP management as achieving a safe level of platelet counts to avoid severe bleeding and minimizing therapy-related adverse effects. More recently, a new class of drugs, rituximab and thrombopoietin receptor (TPO-R) agonists, have been developed for the use in treating patients with ITP including children. The increasing clinical usage of these agents might improve therapeutic approaches and managements for children with ITP.

1 Introduction

Primary immune thrombocytopenic purpura (ITP), the most common isolated thrombocytopenia in children, is characterized by increased platelet destruction in the spleen and by impaired platelet production in the bone marrow [1, 2]. Today, ITP is regarded not as a single disease but collectively as various thrombocytopenic diseases that are commonly involved by immunological mechanisms [1, 3], although its diagnosis yet needs exclusion of any definite disease.

Since the publication of the International Consensus Report [3] and revised American Society of Hematology guidelines [4], the attitude in which pediatrician manage ITP has begun to change. Patients are treated based on symptoms and signs rather than a mere platelet count. The goal of this management is to maintain a safe

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platelet count to a level that will minimize or stop bleeding and to lessen the therapy-related adverse effects of importance for children [5]. More recently, in addition to conventional drugs for ITP, the clinical application of newly developed agents, such as rituximab and thrombopoietin receptor (TPO-R) agonists, has demonstrated the efficacy and safety of these agents for children with refractory or chronic ITP.

This review provides a brief summary of treatment for childhood ITP in the first half and, in the second half, emphasizes the clinical studies of rituximab and TPO-R agonists for primary ITP in children.

2 Management of Children with ITP

In 2009, new terminology for ITP was adopted based on the duration: “newly diagnosed” from diagnosis until 3 months, “persistent” from 3 to 12 months, and “chronic ITP” lasting for longer than 12 months [6].

The International Consensus Report [3] has stated on the management of patients with primary ITP. Bleeding of children with newly diagnosed ITP most commonly shows mucocutaneous symptom (petechiae, ecchymosis, or epistaxis), but only 3% of cases have significant bleeding such as severe epistaxis or gastrointestinal bleeding. In particular, the incidence of intracranial hemorrhage (ICH) is rare (0.1–0.5%), but its prediction is difficult in a practical sense [7]. Severe bleeding is more likely with platelet counts of less than $10 \times 10^9/L$, whereas major bleeding is rarely seen with platelet counts of more than $30 \times 10^9/L$. Most cases of children with newly diagnosed ITP without severe bleeding can be managed using a “watch-and-wait” policy under close observation and with consent of parents. Children with ITP showing significant bleeding must consider hospital admission and treatment if accompanied by marked thrombocytopenia (lower than $20 \times 10^9/L$). The management of children with persistent ITP is fundamentally the same as that for those with newly diagnosed ITP.

The goal of treatment for children with persistent/refractory or chronic ITP is to maintain platelet counts at higher than safety levels and to minimize the therapy-related side effects, especially those associated with long-term administration of corticosteroids. The main first-line treatments include corticosteroids and intravenous immunoglobulin (IVIG) as described below.

In Japan, the guideline previously proposed by the Japanese Society of Pediatric Hematology/Oncology had been used widely for management of childhood ITP [8]. Recently, however, the new consensus of terminology and standardization as well as clinical application of new drugs has engendered an increased need for a revised guideline for children with ITP in Japan.

3 Conventional Treatments [4, 8]

Conventional treatments for ITP include immunosuppressive therapies that primarily aim to reduce platelet destruction (e.g., corticosteroids, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, rituximab, and vinca alkaloids),

immune-modulating agents that prevent macrophage destruction of antibody-coated platelets (e.g., intravenous immunoglobulin and intravenous anti-D), and surgical therapy that prevents platelet sequestration (i.e., splenectomy). However, patients with ITP do not always respond to conventional “immunosuppressive” treatments.

3.1 First-Line Treatments

Corticosteroids and intravenous immunoglobulin (IVIG) are two major conventional drugs used in the first-line therapy for children with ITP in Japan. Children with newly diagnosed ITP presenting with bleeding symptom and $<20 \times 10^9/L$ of platelet counts are treated with prednisolone or prednisone (1–2 mg/kg), which may be effective to induce a response in children within 2–7 days until response. Because of side effects associated with prolonged administration of corticosteroids, they should be used for a maximum of 2 weeks. In a standard way, IVIG is administered at doses of 0.4 g/kg/day (2–5 days) or 0.8–1 g/kg (single day). A rapid increase of platelet is induced in more than 80% of patients usually with a shorter durable response than corticosteroids. With these first-line treatments, approximately 70–80% of children with newly diagnosed ITP are likely to have a complete response within 6–12 months after diagnosis.

However, patients who are severe/refractory or chronic ITP with insufficient response to first-line treatments need careful medical care, in addition to second-line treatments if necessary. Conventional second-line treatments include immunosuppressive agents such as cyclosporine, azathioprine, or mycophenolate. Although splenectomy is another reliable second-line therapy with 70–80% of efficacy at initial response, its application to children has become less frequent because of post-operative risk of infection and, more recently, because of the introduction of new agents such as rituximab and TPO-R agonists in clinical areas.

3.2 Choice of the First-Line Therapy and Chronicity of ITP

When physicians start to treat children with newly diagnosed ITP, the choice of corticosteroids or IVIG might be made dependent on clinical expertise, patient preference, or urgent need to increase platelet counts (generally more rapid response to IVIG than to corticosteroids), rather than on the predictive property for preventing chronic ITP development.

Although the individual course of a child with ITP is difficult to predict, Heitink-Polle et al. assessed therapeutic predictors of chronic ITP using a meta-analysis that revealed significantly fewer chronic ITP patients treated with IVIG (odds ratio: 0.71) than those with other treatments [9]. Moreover, a significantly higher risk for chronic ITP was found for patients treated with a combination therapy of IVIG and standard-dose methylprednisolone (SDMP) than with

other treatments (odds ratio: 2.67). Although this meta-analysis might be useful in clinical practice, these data must be verified with more precise evaluation using with multivariate, not univariate, analysis or prospective clinical trials.

4 Rituximab

Rituximab is a chimeric monoclonal antibody that targets CD20 antigen on the B-cell surface. Rituximab was used at first for treatment of B-cell lymphoma. Then, its target diseases were expanded to autoimmune diseases. Previous reports of rituximab used for children with ITP are shown in Table 1 [10–16], in which only few data are available with regard to the long-term efficacy of rituximab for childhood ITP. Recently, a retrospective study in Japan reported the long-term effects of rituximab for 22 children with refractory ITP, for whom the initial CR rate was as high as 41% (9/22), decreased gradually to a 14% (3/22) relapse-free CR rate at 5 years after the first rituximab therapy [16]. Results of this study also suggest that repeated rituximab administration is a promising therapy because patients who had received multiple courses of rituximab after relapse responded each time without adverse effects. They achieved remission during long-term observation.

As shown in Fig. 1, the downward tendency of relapse-free survival (RFS) after initial response is one of major concerns to therapeutic effectiveness of rituximab [15, 16]. From a long-term follow-up conducted for more than 5 years, Patel et al. showed that 52% (34/66) of initial responders subsequently relapsed. Actually, 28 relapsed within 1 year and 6 relapsed during 1–2 years, but none relapsed after 2 years, suggesting that observation for at least 2 years is necessary to assess the long-term efficacy of rituximab for children with chronic ITP [17].

A recent meta-analysis including 324 pediatric patients showed that a pooled CR (platelet count $>100 \times 10^9/L$) rate and an overall response (platelet count $>30 \times 10^9/L$) rate were 39 and 68%, respectively [18]. Rituximab therapy might be promising for refractory ITP patients, and, therefore, it might offer relief from bleeding symptoms and allow for avoidance of splenectomy. However, infection is a major concern, and there have been reports in children of pneumonia, varicella, and reactivation of hepatitis C [4, 18–20].

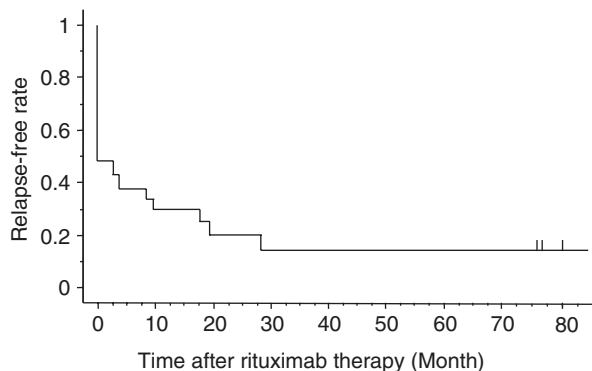
The relationship of clinical variables with response of rituximab and relapse-free factors has been studied [15, 17, 21]. Patel et al. [17] reported that patients showing a higher degree of response continued to remain in remission for a long-term period compared to those with a lesser degree of response (relapse rate within 1 year; 7% (2/28) in CR vs. 40% (4/10) in PR). Nor were significant predictors of splenectomy, gender, or age for response of rituximab and relapse-free factors. Although the efficacy of rituximab was not high, Matsubara et al. indicated that the initial responders to rituximab achieved remission at significantly higher rate, even after relapse than nonresponders did. Consequently, in clinical practice, the initial response is a useful indicator of the subsequent remission rate.

Table 1 Rituximab for children with chronic ITP

Study	No. of patients	Age at ITP diagnosis (year)	Duration before rituximab (month)	Age at rituximab treatment (year)	Times of injection	Duration of observation (month)	Rate of initial response (CR + PR)	Rate of complete response	Relapsed patients after initial response (%)	Duration until relapse	Patients with severe infection	Patients with serum sickness	Reference
1	24		24 (6-120)	NA	4	9	19 (79)	15 (63)	8 (42)	7.5 (3-18)	0	3	[10]
2	22	5.8 (2.5-15.2)	44 (2-27)	NA	1	NA	13 (59)	7 (47)	5 (38)	9 (4-24)	0	0	[11]
4	36	NA	NA (7-145)	11.2 (2.6-18.3)	4	>12	11 (30)	NA	3 (27)	9 (8-11)	0	2	[12, 13]
3	19	NA (3-18)	NA (1-48)	NA	4-6	18	15 (79)	10 (67)	1 (7)	NA	0	0	[14]
5	49	7.4 (0.7-17.6)	21 (1-175)	10.7 (1.2-17.7)	4-6	39.5	34 (69)	26 (53)	13 (38)	4 (1-8)	0	0	[15]
6	22	4.2 (0.3-11.6)	18.5 (2-120)	5 (0.5-20)	1-4	76.8 (62.4-85.2)	11 (50)	9 (41)	8 (72)	(2-26)	0	1	[16]

NA not assessed
Rituximab: 375 mg/m²/dose

Fig. 1 Relapse-free survival rate of subjects who keep continuing first response to the first course of rituximab during long-term follow-up. The *gray-shaded area* of the initial 4 weeks indicates the evaluation period of the initial response to rituximab [16]



Moreover, the rituximab treatment regimen is not necessarily consistent among ITP patients. A recent systematic review pointed that there is no “standard” dose for rituximab treatment in children [18].

4.1 Development of TPO-R Agents

For refractory or chronic children with ITP whose risk of severe bleeding would grow even with the second-line treatments, a strong desire has persisted for therapeutic agents with distinct action mechanisms. The discovery and development of a human recombinant TPO (rh-TPO, the first generation of TPO) proved that the activation of TPO receptor can increase thrombopoiesis of megakaryocytes, facilitating TPO-based therapies as treatment for ITP [22–24].

However, the initial clinical trials demonstrated that healthy volunteers who received rh-TPO became severely thrombocytopenic because of cross-reactivity between autoantibodies to rh-TPO and endogenous TPO. This result led to the development of new agents that stimulate TPO receptor but led to little immunogenic adverse effect. The newly developed TPO-R agonists (the second generation of TPO) belong to either TPO non-peptide mimetics (eltrombopag) or TPO peptide mimetics (romiplostim) that increase platelet production by promoting the maturation of BM megakaryocytes through activation of TPO receptor signaling.

The properties of eltrombopag (daily p.o. medicine) and romiplostim (weekly SC injection) are presented in Table 2. The approved administration of eltrombopag is 50 mg/day initial dose and 75 mg/day maximum in Europe and the United States, but for the East Asian patients, the applied dosage was reduced to 12.5 mg/day initial and 50 mg/day maximum because of ethnic difference of drug responsiveness [25].

In the prospective and randomized studies for adult with chronic ITP, 109 of 135 patients (79%) showed significant increases of platelet counts, decreases of concurrent drugs, and lower demand of rescue therapies [26]. Therapeutic effects were not significantly influenced by prior treatments, previous splenectomy, or pretreatment platelet counts (Fig. 2).

Table 2 Comparative study of hemorrhagic manifestations between pediatric and adult patients with ITP

	Eltrombopag	Romiplostim
Compound	<ul style="list-style-type: none"> • A low-molecular compound activating TPO receptor 	<ul style="list-style-type: none"> • An Fc peptide fusion peptibody binding to TPO receptor
Indication	<ul style="list-style-type: none"> • Adult ITP to which pretreatment is ineffective 	<ul style="list-style-type: none"> • Adult ITP to which pretreatment is ineffective
Dose and effects	<ul style="list-style-type: none"> • Initial dose: 50 mg/day^a • Maximum dose: 75 mg/day • Oral administration (daily) • PLT > 50 × 10³/μL (6 week): 60–81% • Thrombocytopenia after discontinuation • Reduction of combined drugs 	<ul style="list-style-type: none"> • Initial dose: 1 mg/kg/week • Maximum dose: 10 mg/kg/week • SC administration (weekly) • PLT > 50 × 10³/μL (6 week): 63–88% • Thrombocytopenia after discontinuation • Reduction of combined drugs
Affecting factors	<ul style="list-style-type: none"> • No conclusion on children or long-term administration • Little effects of platelet counts, pretreatments, concurrent drug, or splenectomy 	<ul style="list-style-type: none"> • No conclusion on children or long-term administration • Little effects of splenectomy
Adverse effects	<ul style="list-style-type: none"> • Headache, nasopharyngitis, liver dysfunction • Myelofibrosis • Thrombosis 	<ul style="list-style-type: none"> • Headache • Myelofibrosis • Thrombosis
Antibody	<ul style="list-style-type: none"> • No induction of TPO-inhibiting antibody 	<ul style="list-style-type: none"> • Possible neutralizing antibody, but no cross reactivity to TPO

Patients aged 1–5 years: 1.2 mg/kg/day (0.8 mg/kg/day for East Asian patients)

^aPatients weighing less than 27 kg: 37.5 mg/day (25 mg/day for East Asian patients, 12.5 mg/day for Japanese patients)

For romiplostim, the initial dose is 5 μg/kg/week SC and adjusted up to 10 μg/kg/week at maximum with no marked racial difference of drug responsiveness. Similarly to eltrombopag, the efficacy of romiplostim was approximately 80% for adult with chronic ITP. In a randomized and double-blinded clinical trial for 125 patients [27], the percentage of patients who attained reduction or discontinuation of concurrent drugs was 87% for the romiplostim cohort and 38% for the placebo cohort. Moreover, a randomized clinical trial for patients who were refractory ITP without splenectomy, the subsequent execution rate of splenectomy was 9% for the romiplostim cohort and 36% for the standard therapy cohort, suggesting the possible avoidance of splenectomy by incorporating TPO-R agonists to treatment for refractory ITP [28].

The most common adverse effects of TPO-R agonists were headache, although nasopharyngitis and liver dysfunction were also observed for eltrombopag [26, 27, 29–31]. Thrombosis was reported to have a low rate of incidence, but its causal relation remains unclear [28, 31]. As long-term adverse effects, major concerns are the development of myelofibrosis, depletion of hematopoietic stem cells, and induction of other bone marrow abnormalities including malignant diseases. Further investigation of those areas of concern is expected to lead to better understanding.

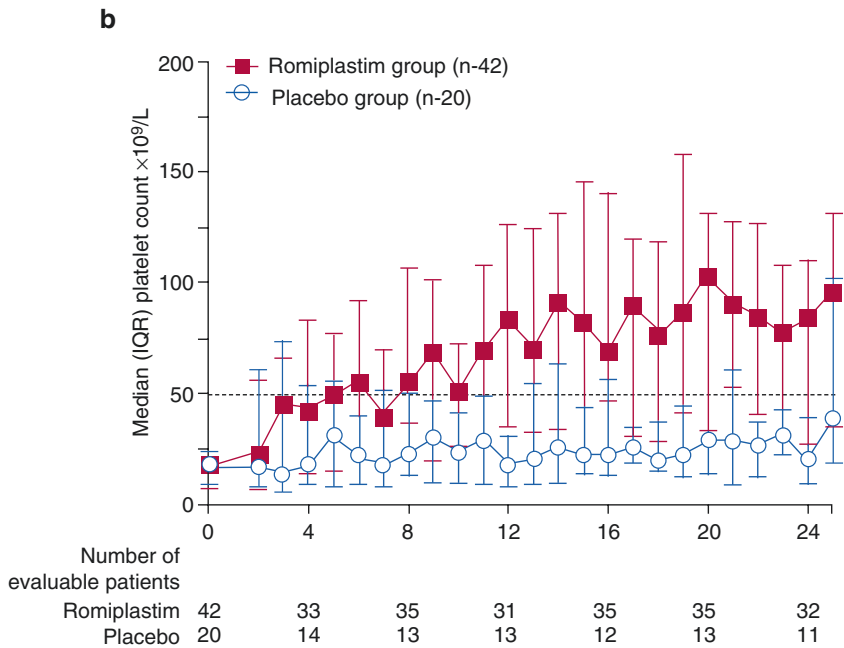
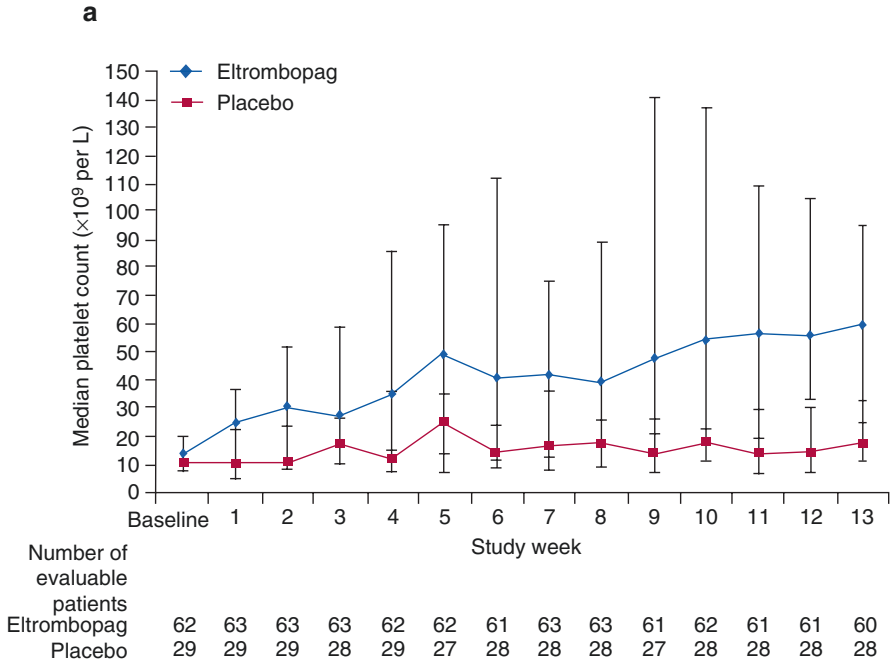


Fig. 2 Prospective randomized clinical trials for children with chronic ITP: (a) the result of study with eltrombopag [37]; (b) the results of study with romiplostim [38]

4.2 Clinical Studies of TPO-R Agonists for Children

Recently, many reports have described the efficacy and safety of TPO-R agonists for children with chronic ITP who had been treated unsuccessfully with the first-line treatments (Table 3) [32–38]. Patients included children (1–17 years old) with chronic/refractory ITP who received romiplostim or eltrombopag at doses adjusted to less than the maximum dose to maintain platelet counts at least $>50 \times 10^9/L$. In 2011, the first randomized clinical trials with romiplostim were reported: short-term observation (12 weeks) for 18 and 22 patients for whom the respective pretreatment duration was 2.4 and 2.5 years [32, 33]. These studies showed that the efficacy to maintain $>50 \times 10^9/L$ of platelet counts without rescue medication was 83.5–88% for patients with romiplostim, as compared to 0% for those with placebo. Nevertheless, the small number of patients and the short-term duration of treatment of these studies might limit the generalization of their conclusions. More recently, a larger study of 62 children (romiplostim, 42; placebo, 20) during 24 weeks of treatment duration revealed that the efficacy of romiplostim was 52% for the romiplostim group as compared to 10% for the placebo group [38]. Another randomized double-blinded and subsequent open-labeled study with eltrombopag has demonstrated its efficacy as 40% for the eltrombopag group, compared to 3% for those of placebo [37]. The efficacy of eltrombopag increased further to 80% (70/87 patients) of efficacy during the following 24 weeks of the open-labeled period. These two recent studies confirmed that both romiplostim and eltrombopag TPO-R agonists are effective for chronic/refractory ITP in children. For these periods, no drug resistance or autoantibody against intrinsic TPO was detected.

Few therapy-associated severe adverse effects leading to forced discontinuation or lethality have been observed, including headache, epistaxis, local pain, cough and vomiting commonly for both drugs, and liver dysfunction for eltrombopag. Although TPO-R agonists are effective and safe for short-term treatment, a retrospective study of children receiving TPO-R agonists for up to 53 months showed that one of 24 patients developed myelofibrosis in grade 2 [35]. The guideline of the American Society of Hematology continues to advise a cautious attitude related to TPO-R agonists for children with ITP [3].

4.3 Long-Term Safety and Discontinuation of TPO-R Agonists

It has been shown that some adult patients remain CR without treatment after discontinuation [39]. Approximately, 30% of adult patients who received these drugs might be able to maintain a safe or normal platelet count after stopping them [5]. Therefore, it remains to clarify whether TPO-R agonists could shorten the period until recovery or facilitate spontaneous cure in a subset of patients with refractory or chronic ITP.

Table 3 Clinical trials of TPO-R agonists for children with ITP

Study	No. of patient	Duration since ITP diagnosis (years)	Age at TPO-R agonist start (year)	PLT count ($\times 10^9/L$)	Splenectomy prior to treatment	Treatment duration (week or month)	Dose (average or range) (romiplostim: $\mu g/kg/week$; eltrombopag: mg/day)	Efficacy (PLT $> 50 \times 10^9/L$)	Treatment-related serious adverse events	Common adverse events	Discontinuation of romiplostim	Reference
Prospective, randomized	22 (romiplostim, 17; placebo, 5)	2.4 (0.6–1.4)	10 (1–17)	13 (2–29)	8 (36%)	12 week	Romiplostim: 5	Romiplostim: 88%; placebo: 0%	no	Headache, epistaxis	no	[32]
Prospective, randomized	18 (romiplostim, 12; placebo, 6)	2.5 (1.2–7.0)	8.5 (2–16)	10.5	0	12 week	Romiplostim: 2	Romiplostim: 83.5%; placebo: 0%	no	Headache, epistaxis, cough, vomiting	For 3 weeks after discontinuation, 50% remained in CR	[33]
Retrospective	10	1.9 (0.8–1.5)	8.5 (2–19)	n.a.	20%	9 month (3–36)	Romiplostim: 4–10	50%	no	Headache, local pain, mood disorder	Three remained in CR	[34]
Retrospective	33 (romiplostim, 21; eltrombopag, 12)	Romiplostim: 4.0; eltrombopag: 5.0	Romiplostim: 11.4 (1.6–19); eltrombopag: 14.5 (3–19)	Romiplostim: 20; eltrombopag: 25	Romiplostim: 2 (9%); eltrombopag: 1 (8%)	Romiplostim: 6–44 month; eltrombopag: 23–53 month	Romiplostim: 8.1; eltrombopag: 66.7	82%	no	Rash, headache, nausea, epistaxis	7 (21%) remained in CR after discontinuation	[35]
Prospective	24	2.4 y (1–14)	10 (1–17)	13 (2–29)	8 (36.4%)	167 week (12–242)	Romiplostim: 6.0 (3.1–9.7)	84.6%	no	Headache, respiratory infection, pyrexia	Several patients	[36]

Prospective, randomized	92 (eltrombopag, 63; placebo, 29)	Eltrombopag: 2.8; placebo: 3.4	Eltrombopag: 9.4 (8.2–10.5); placebo: 9.8 (8.3–11.3)	<30 × 10 ⁹ /L	Eltrombopag: 4 (6%); placebo: 0 (0%)	Double-blinded: 12 week; open-labeled: 24 week	Eltrombopag: 42.8–67.7 (East Asians: 37.2–58.9)	Eltrombopag: 40% (open-labeled: 80%); placebo: 3%	Eltrombopag: 8%; placebo: 14%	Nasopharyngitis, rhinitis, epistaxis, cough, headache, liver dysfunction	n.a.	[37]
Prospective, randomized	62 (romiplostim, 42; placebo, 20)	Romiplostim: 1.9 (1.0–4.2); placebo: 2.2 (1.5–3.7)	Romiplostim: 10 (6–14); placebo: 7.5 (6.5–13.5)	<30 × 10 ⁹ /L	Romiplostim: 1 (2%); placebo: 1 (5%)	25 week	Romiplostim: 3.9 (2.4–7.3)	Romiplostim: 52%; placebo: 10%	Romiplostim: 1 (headache, thrombocytosis)	Contusion, epistaxis, headache, thrombocytosis	n.a.	[38]

n.a. not available

5 Conclusion

In these years, with advances in understanding of pathophysiology of ITP and development of new therapeutic agents for ITP, there have been dynamic changes in the management and therapeutic approaches for children with ITP. However, from the viewpoint of children in the process of hematological and immunological development, further investigation needs to clarify their therapeutic role and long-term safety of those new agents for children with primary ITP.

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