CLINICAL INVESTIGATION

Will thrombopoietin receptor agonists become a treatment option for pediatric chronic immune thrombocytopenia in the future?

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Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count and increased bleeding tendency. Most children with ITP spontaneously recover. However, children with severe bleeding may require treatment. Traditional treatments such as corticosteroids or splenectomy are often associated with increased risks of infections. Currently, there is evidence that platelet production is suboptimal in many chronic ITP patients and stimulation of platelet production by thrombopoietin receptor agonists (TpoR-As) is effective in raising the platelet counts. However, these clinical studies were conducted mainly in chronic ITP patients, age 18 or above, and TpoR-As are not yet licensed for use in children. Clinical trials are now being conducted to investigate the efficacy and safety of TpoR-As in pediatric ITP.

Keywords: immune thrombocytopenia • pediatric ITP • thrombopoietin receptor agonists

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count and increased bleeding tendency. It affects about 5 in 100,000 children. Most children with ITP and bleeding get better without drug intervention. However, some patients may have severe bleeding requiring treatment and up to 20% may have persistent disease. Traditionally, the mechanism of ITP was thought to be due mainly to immune-mediated destruction of the antibody-coated platelets. Therefore, treatments are aimed mainly at suppressing the production of the antiplatelet antibodies using immunosuppressive agents such as corticosteroids, cytotoxic drugs or at reducing platelet destruction in the spleen by splenectomy. Treatments with immunosuppressive agents often have only transient effects and were often associated with serious side effects such as increased risks of infections. Currently, there is evidence that platelet production is suboptimal in many patients with chronic ITP and serum thrombopoietin (TPO) levels are inappropriately low or only near normal in these patients. Many clinical studies have shown that stimulation of platelet production by thrombopoietin receptor agonists (TpoR-As) is effective in raising the platelet counts in many patients with chronic ITP. Two thrombopoietin receptor agonists – romiplostim (AMG-531, Nplate; Amgen, Thousand Oaks, CA) and eltrombopag (Revolade, Promacta; GlaxoSmithKline, Brentford, UK) – have now been licensed for the treatment of ITP. However, these clinical studies were conducted mainly in chronic ITP patients, age 18 or above, and these two drugs are not yet licensed for use in the pediatric population. Clinical trials are now being conducted to investigate the efficacy and safety of TpoR-As in children with ITP. Based on the long-term safety data in adult ITP and the efficacy data from the ongoing clinic trials in the pediatric ITP population, this article discusses the potential of thrombopoietin receptor agonists as a treatment option for pediatric ITP

Childhood ITP

ITP of childhood is characterized by isolated thrombocytopenia with platelet count $<100 \times 10^9$/l [1,2]. According to studies in United States and Europe, the incidence of

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childhood ITP is approximately 4–8 cases per 100,000 children per year with peak prevalence in children aged 2–4 years [3–5]. Childhood (age 10 or less) ITP affects boys and girls in an approximately 1:1 ratio as opposed to a female predominance in adult ITP [6]. Spontaneous remission occurs in over 40–60% of cases within three months and more than half of the children recover within 4–8 weeks [3–5]. A few children have persistent ITP, which is defined as thrombocytopenia and symptoms persisting for more than 3 months but less than one year. Thrombocytopenia continuing for more than 12 months from initial presentation is defined as chronic ITP [1,2] and 20% of childhood cases eventually become chronic ITP. The cause is unknown in most cases, but it is often preceded by a viral infection or following immunizations [7]. Hemorrhage, particularly intracranial hemorrhage is the most serious complication. Patents with platelet counts fewer than 30.0 × 10^9/l had an estimated rate of fatal hemorrhage between 0.0162 and 0.0389 cases per patient-year [8]. Bone marrow examination is usually not indicated for children presented with only isolated thrombocytopenia and a normal physical examination besides petichiae and ecchymosis. However, if there is involvement of other cell lineages or if splenomegaly or lymphadenopathy is present, bone marrow examination may be indicated.

Pathophysiology

Many ITP children had IgG and IgM autoantibodies directed against platelet glycoproteins such as the Gp IIb/IIIa and Gp Ib/IX complexes as well as a variety of platelet epitopes [9]. These antibodies result in accelerated clearance of the antibody-coated platelets by the spleen and the macrophage-phagocytic system [10]. Recent data showed that $CD4^+CD25^+$ regulatory T cell is also decreased in patients with ITP [11,12].

Both *in vitro* and *in vivo* platelet production studies suggested that in many ITP patients, platelet production was inadequate or suboptimal [13–15]. Besides accelerating platelet destruction, the antiplatelet antibodies may also interfere with megakaryopoiesis and platelet egress from the bone marrow. Plasma from certain pediatric patients containing anti-Gp Ib/IX autoantibodies had been shown to decrease megakaryocytopoiesis while control normal AB plasma and plasma from ITP cases mediated by autoantibodies directed against other platelet epitopes had no such inhibitory effects [16,17]. Plasma from pediatric patients containing only Gp IIb/IIIa autoantibodies had been shown to have either inhibitory, stimulating or no effects on megakaryocytopoiesis.

These data highlighted the heterogeneous nature of ITP and may partly explained the unpredictable clinical course and variable response to treatment.

Current guidelines & treatments

Children who have platelet counts >30 × 10^9/l and who are either asymptomatic or having only minor purpura usually do not require specific treatment to raise the platelet counts. Children who have platelet counts <20 × 10^9/l associated with significant mucous membrane bleeding or those children with platelet counts <10 × 10^9/l and minor purpura should receive specific treatment [1].

Glucocorticoids and intravenous immunoglobulin (IVIg) are the current mainstays of medical therapy. However, prolonged steroid use is associated with significant side effects such as osteoporosis, glaucoma, hypertension, diabetes, cataracts, loss of muscle mass and an increased risk of infection. IVIg may result in a more rapid response than steroids and is recommended in the actively bleeding situations. Some patients may require repeated courses of IVIg and this can be expensive.

Splenectomy is an accepted and effective treatment of children with chronic ITP, with a prolonged response rate of 60–88% [18–20]. The irreversible nature of this procedure, the increased risk of sepsis with a mortality rate of up to 1.6% [21], the absence of reliable predictors of the effect of splenectomy and the potentials of spontaneous remission deter many patients opting for splenectomy.

Splenectomy is often delayed in children due to the associated risks [22]. The risk is overwhelming post splenectomy sepsis is greatest in patients younger than 5 years of age and most physicians prefer postponing splenectomy in this age group. Since spontaneous remissions occur in up to 80% of childhood ITP [3–5], the current guideline is splenectomy should be avoided in the first year unless in cases of serious bleeding refractory to treatment with IVIg/steroids. However, there was observation in some retrospective study that patients with good responses to IVIg were likely to have good responses to splenectomy, whereas patients with poor responses to IVIg were unlikely to benefit from splenectomy [23]. Therefore, those children with refractory ITP who require second-line therapy may have more harm than benefits from splenectomy. Better predictors of splenectomy failure are needed for these children [24].

Rituximab (MabThera; Roche, Basel, Switzerland) is a chimeric monoclonal antibody specific for the CD20 antigen expressed by mature B-cell. It was licensed initially for the treatment of non-Hodgkin B-cell lymphoma in the early 1990s. Rituximab causes the elimination of B cells, including the B cell clones that produce the autoreactive antibodies. Therefore, it has also been widely used in the treatment of autoantibody-mediated disorders such as rheumatoid arthritis,

system lupus and ITP [25–27]. Patel *et al.*, summarizing 17 studies, totaling 492 children and adult ITP patients treated with rituximab (375 mg/m^2 × 4 doses), found an overall response rate of around 60% with sustained response rates between 20 and 35% [28]. Seventy-two selected adults and 66 children who had achieved complete response (platelets >150 × 10^9/l) or partial response (platelets between 50–150 × 10^9/l) with rituximab were followed up for prolonged period to assess the duration of their response. The 5-year persisting response rates were 21% in the adult group and 26% in the children group. Children did not relapse after 2 years from initial treatment whereas adults did. Persistent hypogammaglobulinemia following rituximab has been reported in up to 23% of patients with rheumatoid arthritis [29]. Four cases of neutropenia, hypogammaglobulinemia, and SLE (32–48 months postinfusion in all four cases) were observed in the 138 rituximab treated ITP patients reported by Patel [28]. Other reported toxicities of rituximab use included neutropenia, hematologic malignancies, and progressive multifocal leucoenceplaopathy [30]. Hypogammaglobulinemia could be a result of CVID developing subsequent to ITP. Although this complication is infrequent and not associated with severe infection so far, survey of gammaglobulin levels after rituximab treatment may be warranted yearly for at least 3–5 years to assess the need for prophylactic IVIg maintenance therapy [29].

Since prolonged high doses steroids use, splenectomy and rituximab have associated persistent side effects and many children with ITP eventually go into remission, it is the author's opinion that there is a need for a safe and effective short-term treatment alternative.

TpoR-A

Impaired platelet production was observed in many ITP patients. Recent studies also showed that serum thrombopoietin (Tpo) levels were inappropriately low or only near normal in many thrombocytopenic ITP patients [31]. Therefore, stimulation of platelet production by thrombopoietin (Tpo) or Tpo mimetics may be helpful in ITP patient refractory to currently available treatments. Recombinant thrombopoietin had been shown to increase platelet counts in ITP patients [32,33], but this was associated with production of autoantibodies cross-reacting with neutralizing endogenous thrombopoietin. These anti-thrombopoietin antibodies caused severe prolonged thrombocytopenia that persisted for months or years after discontinuation of recombinant thrombopoietin [34,35]. Subsequent research led to the development of novel agents that bear no sequence homology to the native thrombopoietin, but can activate the thrombopoietin receptor. These agents are known as TpoR-As. Two TpoR-As, romiplostim (AMG-531, Nplate; Amgen, Thousand Oaks, CA) [36] and eltrombopag (Revolade, Promacta; GlaxoSmithKline, Brentford, UK) [37], have now been licensed for the treatment of ITP.

Eltrombopag

Eltrombopag is a small molecule, nonpeptide thrombopoietin receptor (Tpo-R) agonist. It was identified by high-throughput screening of small-molecule compounds with hematopoietic cell lines expressing with the human Tpo-R [37]. Eltrombopag caused a dose-dependent increase in platelet counts in healthy volunteers, but did not affect agonist-induced platelet aggregation or activation [38,39]. It has excellent oral bioavailability with a peak concentration 2–6 h after oral administration. The recommended starting dose is 50 mg daily. It has to be taken 4 h before or after antacids, dairy products or food products containing polyvalent cations because these may significantly reduce absorption. A lower starting dose of 25 mg daily is recommended for East Asian population because of the higher concentrations achieved for the same dosage. Eltrombopag selectively binds to the transmembrane domain of the thrombopoietin receptor and activates the Janus Kinase/Signal Transducer and Activator of Transcription signaling pathway

Romiplostim

Romiplostim is a fusion protein consisting of the constant regions of the immunoglobulin chains and a thrombopoietin receptor binding domain. It binds to the extracellular region of the thrombopoietin receptor. It also activates the Janus Kinase/Signal Transducer and Activator of Transcription signaling pathway. It has no sequence homology with endogenous thrombopoietin and is administered as a once weekly subcutaneous injection [40]. Like eltrombopag, it caused a dose-dependent increase in platelet counts in healthy volunteers and did not affect agonist-induced platelet aggregation or activation.

Clinical efficacy in adult ITP

Numerous clinical studies had been conducted to evaluate the safety and efficacy of eltrombopag and romiplostim in the treatment of adult ITP patients [40–47].

Most of these trials enrolled adult ITP patients with disease duration of 6 months or longer, and who had either failed at least one prior therapy, including splenectomy, or had relapsed within 3 months of previous therapy. The platelet counts were <30 × 10^9/l at the time of enrollment. Both eltrombopag and romiplostim were able to raise the platelet counts to

>50 × 10^9/l in 60–90% of the treated subjects, able to reduce bleeding symptoms, reduce or discontinue concomitant ITP medications in 40–50% of patients and improve health-related quality of life [40–47].

In patients responding to eltrombopag treatment, the platelet counts usually started to increase after 1 week of treatment, peaked around the second week and maintained at a steady level throughout the study as long as the patients continued on drug treatment. Upon discontinuation of eltrombopag treatment, the platelet counts will return to the baseline level within 2 weeks in most patients. There is a theoretical worry that in some patients, the platelet counts may even drop below pretreatment level with worsening of the bleeding symptoms (rebound thrombocytopenia). However, similar proportions (7–10%) of patients in the eltrombopag or placebo groups had transient decreases in platelet counts to both less than 10 × 10^9/l and at least 10 × 10^9/l below baseline [45,46]. Response to eltrombopag was not affected by the splenectomy status, baseline platelet counts, or whether the patients use concomitant ITP medications.

Similar observations were reported with romiplostim responding patients with the platelet counts increasing after 1–2 weeks of treatment, reaching a peak by the third week and maintained throughout the remaining weeks. Following romiplostim stoppage, the platelet counts returned to baseline levels within 2 weeks in most patients. Again, there was similar incidence of rebound thrombocytopenia in romiplostim and placebo treated subjects following treatment discontinuation [42,43].

For most patients, the platelet counts would drop to baseline levels within 2 weeks of discontinuation of Tpo-R agonist treatment. However, about 3–4% of ITP subjects were able to maintain a satisfactory platelet counts for a prolonged period after a brief period of treatment with TpoR-A. In the EXTEND study, 13 out of 302 subjects (4%) had prolonged response off eltrombopag therapy. The median duration of the prolonged response was 54.9 weeks. The median time on eltrombopag was 258 days (14–1107). All 13 patients had a long history of ITP (25.8 months, range 9–73 months), and 5 patients had splenectomy [48]. Similarly, 9/291 patients from an open-label romiplostim extension study had hemostatic platelet counts maintained for at least 6 months off romiplostim. The duration of romiplostim therapy was 37–139 weeks [49].

One study of 54 patients looked at the proportion of patients who maintained a prolonged response after TpoR-As discontinuation [50]. Eighteen patients received eltrombopag, 22 romiplostim and 14 received both TpoR-As sequentially for an overall median time of 10 months (range: 1–70 months). The initial overall response rate on TpoR-A was 81.5% (44/54). Eight out of the 54 patients (15%) had a median prolonged response of 13.5 months (range: 5–27 months) after TpoR-A discontinuation. These eight patients had a median ITP duration of 103 months (13–297) before TpoR-As treatment and had received a median of 5 lines of treatment (2–12). Interestingly, three out of these eight patients received only a very short course (<1 month) of TpoR-A. No predictive factors of sustained response were noted.

Safety profile

Both eltrombopag and romiplostim have good safety profile [42–46]. From published data, adverse events were primarily grade 1–2 in severity. About 10% of eltrombopag-treated patients had elevated bilirubin and serum aminotransferase levels. In some cases, the elevations were more than five times the upper limits of normal. The elevated bilirubins were uncojugated bilirubins. All these hepatobiliary laboratory abnormalities (HBLAs) were reversible upon eltrombopag discontinuation and in many patients, they resolved spontaneously while the patients continued with eltrombopag therapy. Moreover, in some patients, the HBLAs did not recur upon restarting eltrombopag.

Thromboembolic risk

In the EXTEND study [47], 19 out of 302 (6%) patients receiving prolonged eltrombopag treatment experienced 25 confirmed or suspected thromboembolic events with an incident rate of 3.02/100 patient years. Deep vein thrombosis (n = 10) and myocardial infarction (n = 7) were the most common thromboembolic events. The frequency of thromboembolic events in patients treated with eltrombopag in EXTEND study is similar to that reported for the general ITP patient population not receiving TpoR-A [51]. Eighty-four percent of these patients (16/19) experienced the thrombotic event at a platelet count lower than the maximum platelet count achieved during eltrombopag treatment and there was no correlation between platelet count levels and the occurrence of thromboembolic events. In nearly half of the cases, thromboembolism occurred at a platelet count below 150 × 10^9/l and in about one-third of the cases, the platelet counts were <50 × 10^9/l at the time of thromboembolism. In some patients, thrombosis occurred at platelet counts <10 × 10^9/l. All 19 patients had at least one or more thromboembolic risk factors such as hypertension, smoking, prolonged hospitalization following surgery, or obesity. There was also no relation between the duration of eltrombopag treatment and the occurrence of thromboembolic events. The median time to the onset of thrombosis was 229 days (range 1–981 days). Similar observations

were made with romiplostim and the overall incidence of thrombosis is around 5.5% [42,43].

So far, the clinical data did not suggest an increased risk of thrombosis with Tpo-R agonist therapy in ITP patients.

Myelofibrosis

There is a wary that thrombopoietin receptor agonists may increase reticulin deposition in the bone marrow and increase the risk of myelofibrosis [52]. In an open-label extension study [43], 16 out of 142 patients who were treated with romiplostim for a mean of 69 weeks (longest up to 156 weeks) had bone marrow examinations performed. Eight samples had increased reticulin, but clonal abnormality was not detected. In two patients, follow-up bone marrow examinations showed improvement of reticulin score in one subject and no change in the other. In a Phase IV open-label study evaluating changes in bone marrow morphology in adult ITP patients receiving romiplostim [53], 37 out 50 patients (74%) had MF-0 and 13 patients (26%) had MF-1 at enrollment. After 1 year follow-up, 35 subjects had repeat biopsies, only two patients experienced an increase of MF-0 to MF-2. None had collagen deposits.

In another long-term romiplostim study of 292 patients, 41 bone marrow biopsies were performed in 38 patients. Increased bone marrow reticulin was observed in 12 biopsies from 11 patients. It resolved spontaneously within 4 months in one patient and remained stable in eight patients at the end of the 5-year follow-up period. The other patients were lost in follow-up [54].

In the EXTEND study, bone marrow biopsies were obtained from 113 patients treated with eltrombopag [47]. The specimens were processed and stained for reticulin by a central laboratory and reviewed by a central pathologist. No clinically relevant increases in reticulin deposition were observed with up to 4.75 years of treatment. Two patients had maximum reticulin grade MF-2 after >24 months on treatment. Neither experienced any adverse effect or abnormality in hematologic parameters potentially related to bone marrow function.

So far, there are clinical data to suggest that TpoR agonists increase the risk for developing or worsening myelofibrosis. However, the follow-up period is still rather short, and more long-term data are needed.

Antithrombopoietin antibodies formation

Both eltrombopag and romiplostim have no sequence homology with thrombopoietin. For eltrombopag, there was no reported incidence of anti-Tpo antibodies. For romiplostim, there were two cases of anti-romiplostim antibody [43], but no reported incidence of antithrombopoietin antibody. In these two cases, the antiromiplostim antibodies were not clinically significant.

However, all the above clinical studies regarding safety and efficacy of TpoR agonists were conducted mainly in chronic ITP patients, age 18 or above, and these two drugs are not recommended for use in the pediatric population. Ongoing trials are now investigating the efficacy and safety of TpoR agonists in children with ITP.

Clinical studies in pediatric ITP

A retrospective analysis of 32 ITP children who had been treated with thrombopoietin receptor agonists in a nonstudy setting showed that around 80% of the treated children showed an increase in platelet counts to ≥50 × 10^9/l and at least 20 × 10^9/l above baseline for two consecutive weeks [55]. Twenty-one children received romiplostim and 12 received eltrombopag with response rate of 86 and 75%, respectively. The duration of romiplostim and eltrombopag treatment ranged from 6 to 44 months and 23 to 53 months, respectively. One patient on eltrombopag experienced a provoked deep-vein thrombosis at the site of ankle fracture. Twenty-four bone marrow examinations had been performed, 40% after the children had been on TpoR-A for more than 2 years. Twenty-three out of the 24 bone marrows biopsies performed were normal (MF grades 0–1). One was MF-2. Tachyphylaxis to treatment was not observed.

In one randomized study, 22 patients with ITP of ≥6 months duration were stratified by age 1:2:2 (12 months to less than 3 years; 3 to less than 12 years; 12 to less than 18 years) to receive weekly subcutaneous injections of romiplostim (n = 17) or placebo (n = 5) weekly for 12 weeks [56]. The starting dose of romiplostim was 1 μg/kg and adjusted to maintain platelet counts between 50 × 10^9/l and 250 × 10^9/l. The primary end point was platelet counts >50 × 10^9/l for two consecutive weeks. This primary end point was achieved by 15/17 (88%) patients in the romiplostim group as compared with none in the placebo group ($p = 0.0008$). The median weekly dose of romiplostim was 5 μg/kg.

In another study, 18 chronic ITP patients who had failed to respond to relapsed from two or more conventional treatments were randomized in a 2:1 ratio to receive either romiplostim or placebo for 12 weeks [57]. Romiplostim was started at 1 μg/kg/week, escalated to 5μg/kg/week, and then tapered to maintain platelet counts between 50 × 10^9/l and 250 × 10^9/l. The median age of the children was 8.5 years, and the median baseline platelet counts were 10.5 × 10^9/l. The median weekly dose of romiplostim was 2 μg/kg.

Eighty-three percent (10/12) of the patients in the romiplostim group achieved the efficacy end point with platelet counts greater than 50 × 10^9/l.

The PETIT study (TRA108062) was a Phase II, placebo-controlled clinical trial study of eltrombopag treatment for childhood persistent and chronic ITP [58]. The primary end point was the proportion of subjects achieving platelet counts ≥50 × 10^9/l at least once (without rescue) between days 8 and 43 of the study.

Forty-five and 22 subjects were randomized to receive eltrombopag and placebo, respectively. The primary end point was achieved by 62.2 and 31.8% of the eltrombopag- and placebo-treated subjects, respectively (odds ratio 4.31; 95% CI: 1.4–13.3; p = 0.011). Eltrombopag-treated subjects reported fewer grade 2–4 bleeding on the World Health Organization scale (27 vs 59%) and less requirement of rescue therapy (13.3 vs 50%). Adverse events and serious adverse events were similar in both groups. The most common adverse events reported were headache occurring in 29.5 and 42.9% of eltrombopag- and placebo-treated subjects respectively and upper respiratory tract infection (15.9 vs 9.5%). Grade 3/4 events occurred in 11 and 19% of eltrombopag and placebo subjects, respectively. Sixty-five out of the 67 subjects subsequently enter the open-label phase. Three subjects withdrew due to grade 3 HBLAs which resolved completely after stopping eltrombopag.

The PETIT-2 study was a Phase III study enrolling 92 children from 38 centers in 14 countries [59]. All patients were 18 years old or younger, had chronic ITP for at least 12 months and had baseline platelet counts <30 × 10^9/l. They had failed at least one prior treatment. Subjects were stratified into three cohorts according to their age: 12–17 years (Cohort 1), 6–11 years (Cohort 2), and 1–5 years (Cohort 3). In the first part of the study, the subjects were randomized in a 2:1 ratio to receive either eltrombopag or placebo for 13 weeks. Treatment was unblinded at week 13 and all subjects then began 24 weeks of open-label treatment with eltrombopag. Subjects aged 6–17 years and weighing ≥ 27 kg started eltrombopag treatment at 50 mg daily, while those weighing <27 kg started treatment at 37.5 mg daily. Subjects aged 1–5 years started eltrombopag treatment at 1.2 mg/kg. Starting dosage at all ages was reduced by 50% for East Asian subjects. Subsequent eltrombopag dose was adjusted based on platelet counts and could be increased to a maximum of 75 mg daily. The primary end point was an increase in platelet count to 50 × 10^9/l or more for at least 6 out of 8 weeks between weeks 5 and 12. Ninety-two subjects were enrolled: 33 to Cohort 1, 39 to Cohort 2 and 20 to Cohort 3. Sixty-three and 29 subjects were randomized to eltrombopag and placebo, respectively.

In the first part of the study, almost 40% of eltrombopag-treated subjects maintained a consistent platelet count >50 × 10^9/l for 6 out of 8 weeks between weeks 5 and 12, compared with 3% of patients in the placebo group (p <0.001). Response rates were similar across the three age cohorts with 39% response rate for Cohort 1, 42% for Cohort 2, and 36% for Cohort 3. Three quarters of the subjects on eltrombopag achieved platelet counts ≥50 × 10^9/l at least once during the first 12 weeks as compared with a 20.7% response rate in the placebo group (p < 0.001). Clinically significant bleeding (World Health Organization grade 2–4) was present at baseline in 28.6% of eltrombopag-treated subjects and 13.8% of placebo-treated subjects. At the end of the first phase of the study, grade 2–4 bleeding was present in 4.8% of eltrombopag subjects and 6.9% of placebo subjects. In the second open-label phase, 80.5% of subjects achieved platelet counts ≥ 50 × 10^9/l at least once during the 24-week period. Fifty and 66% patients on eltrombopag experienced reduced bleeding symptoms by week 12 and at the end of the study, respectively. Sixty-one percent of eltrombopag-treated patients were able to stop or reduce their concomitant ITP medications. The median daily doses during the open-label phase were 67.7, 56.9 and 42.8 mg for Cohorts 1, 2 and 3, respectively.

The most common adverse events were nasopharyngitis, rhinitis, cough and respiratory tract infection. Grade 3/4 adverse events were reported in 12.7% of eltrombopag and 10.3% of placebo subjects. Two children had abnormal liver tests who returned to normal after stopping the drug. Four children discontinued eltrombopag due to a lack of response.

The clinical data so far suggested that TpoR-A treatment of children with ITP appeared to be safe and effective.

Unanswered questions

While TpoR-A appears to be safe, effective and tolerable in children with ITP, there remain several unanswered questions.

Currently, TpoR-As are licensed only for use in adult ITP cases. In pediatric ITP, shall we limit the off-label use of TpoR-A as a last resort only to those children who are refractory to current treatments including steroids, IVIg, splenectomy, cytotoxic drugs and perhaps rituximab or not at all?

For refractory pediatric ITP cases with significant bleeding symptoms, off-label use of TpoR-A may be worth considering.

- What are the long-term effects on growth, development and reproductive functions?
  - Since almost all of the children treated so far had only been treated and followed for a short period of time, majority of them less than 5 years, whether TpoR-A has any adverse effects on growth and development remains a major concern.
- What is the risk of myelofibrosis?
  - So far the clinical data in adults did not suggest an increased risk of myelofibrosis, but the follow-up period is still rather short, and whether the children bone marrow is more vulnerable remains to be determined.
- What is the optimal duration of treatment in children ITP?
  - In most ITP patients treated with TpoR-A, the platelet counts will drop back to the baseline levels following discontinuation of TpoR-A treatment. However, since there is a high rate of spontaneous remission in childhood ITP, the long-term safety of prolonged use of TpoR-A in children is unknown, and TpoR-A in children should only be used in a research setting or off-label in the refractory case, perhaps once bleeding symptoms are controlled, one should have repeated attempts to taper the child off the drug.
- What is the optimal starting dose of TpoR-A in children with ITP?
  - Shall we start with a low dose and gradually titrating up? Or since only those children with serious bleeding symptoms not responding to first-line therapy should receive treatment with TpoR-A and it usually takes at least 1–2 weeks of TpoR-A treatment before platelet counts start to increase, shall one rapidly escalate the dose to the maximum recommended dose to control the bleeding and then taper down?

The answers to these questions require well-designed randomized double-blinded studies.

Conclusion

The clinical data so far suggested that TpoR-A treatment is effective in raising the platelet counts and reduce bleeding symptoms in children with ITP. TpoR-As have a good safety profile and no clinical significant side effects had been reported so far.

Future perspective

In the near future, many more safety and efficacy data on the use of TpoR-A in pediatric ITP will be available and there is a good chance that these drugs will be licensed for use in pediatric ITP.

Until such time, for ITP children with serious bleeding symptoms requiring treatment, steroids and IVIg are still the first line of treatment. For those children who fail to respond to steroid and IVIg, or those with relapsing course requiring high-dose maintenance steroids or frequent repeated IVIg infusion, alternative treatments are needed. In view of the absence of predictive factors for splenectomy failures, the irreversible nature of splenectomy and the long-term risks of infection, splenectomy should be delayed for as long as possible. Similarly, rituximab treatment may result in persistent hypogammaglobulinemia that may be a potential long-term concern.

TpoR-A so far appears to be a safe and effective short-term treatment option to support the patient while awaiting spontaneous remission. In view of the unknown long-term side effects of TpoR-A in children, patients should be given the minimal effective dose aiming at platelet counts sufficient to reduce the bleeding symptoms to a minimal and for a minimal duration. For refractory ITP children with persistent significant bleeding symptoms after 2–3 months of high-dose steroid/IVIg therapy, one may start TpoR-A therapy. In responding cases, the platelet counts and bleeding symptoms usually improve within 2–4 weeks. For each child after resolution of the bleeding symptoms, one may attempt to taper off the TpoR-A over a period of 2–6 weeks. Some children may have a prolonged response after discontinuation of TpoR-A. In some patients, the platelet counts will drop to the baseline levels with recurrence of the bleeding symptoms. In these situations, one can usually restart the patients on the previous effective dose and the patients usually respond promptly. The REPEAT studies in adult ITP [60] and case studies in pediatric ITP suggest that tachyphylaxis seldom occurs with repeat dosing. For those children responding to repeated TpoR-A treatments, again one will make a second or even third attempt to taper the patient off therapy.

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Executive summary

- TpoR-A treatment is effective in raising the platelet counts and reducing bleeding symptoms in children with immune thrombocytopenia (ITP).
- TpoR-A treatment in children is well tolerated. Safety profile is similar to that observed in adult patients.
- Longer follow-up is needed to address effects on growth and development.
- TpoR-A is not yet licensed for use in pediatric ITP.
- Most children with ITP and bleeding get better without drug intervention.
- Glucocorticoids and intravenous immunoglobulin (IVIg) are the current mainstays of medical therapy for children with severe bleeding requiring treatment.
- After licensed for use in pediatric ITP, for those children with severe bleeding symptoms not responding to current first-line treatments such as steroids/IVIg, TpoR-A may be a good short-term treatment option to support the patients while awaiting spontaneous remission.
- In view of the unknown long-term side effects of TpoR-A in children, patients should be given the minimal effective dose aiming at a platelet count sufficient to reduce the bleeding symptoms to a minimal and given for a minimal duration.

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