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Efficacy of romiplostim in the treatment of ITP in children: a meta-analysis

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Abstract. – OBJECTIVE: We aimed to analyze the efficacy and safety of romiplostim in the treatment of primary immune thrombocytopenia (ITP) in children.

MATERIALS AND METHODS: PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Chinese biomedical literature database (CBM), Chinese Journal Full Text Database (CNKI), Wanfang and VIP database were searched. The bibliography was screened according to the inclusion and exclusion criteria and the target literature was selected. The data were extracted, and the quality of included literature was evaluated. RevMan 5.3 software was used to carry out the meta-analysis. The rate of effective, adverse and bleeding events was collected, and meta-analysis was performed.

RESULTS: 3 out of 43 papers met the inclusion criteria. Meta-analysis showed that there was a statistical significance in effective rate and median time to platelet rise to response criteria of in romiplostim group, RR=5.05, [95% CI (2.21, 11.53), $p<0.01$] and RR=9.67, [95% CI (1.89, 49.46), $p<0.01$]. Similar results occurred in the rate of adverse event and serious adverse event, [RR=0.95, 95% CI (0.69,1.31), $p>0.05$] and [RR=1.65, 95% CI (0.53,5.31), $p>0.05$]; bleeding event of the two groups was similar [RR=1.27, 95% CI (0.92,1.75), $p>0.05$].

CONCLUSIONS: On the aspect of treating ITP, romiplostim is more effective and safer than placebo.

Key Words:
Romiplostim, Immune thrombocytopenic, Children, Meta-analysis.

Introduction

Primary immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenic purpura, is the most common hemorrhagic disease in children, accounting for 1/3 of hemorrhagic diseases[1]. ITP is one of the most common causes of acute thrombocytopenia in children[2]. Its occurrence rate is about 4-5/100,000[3]. The pathogenesis of primary immune thrombocytopenia is mainly due to autoantibody-mediated platelet destruction, which results in thrombocytopenia in ITP patients. In recent years it has been found that in the pathogenesis of ITP, platelet deficiency is one of the most important mechanisms of ITP pathogenesis[4]. At present, corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin (anti-D) are recommended by many guidelines or consensus for the first-line ITP therapy [5-9]. The main purpose of the treatment is to prevent severe bleeding, not to raise PLT to normal[10-11]. Although these treatments are effective for most patients, there are many adverse reactions. After glucocorticoid treatment adverse reactions such as appetite, weight gain, temporary hyperglycemia, and hypertension and abnormal behavior used to be noticed. That's why children should avoid long-term use[8]. IVIG infusion may also lead to the hepatitis virus, HIV and other pathogens spread risks[12].

In recent years, with thrombopoietin receptor agonist, romiplostim has become a new choice for the treatment of ITP. Romiplostim is the first small molecule peptide TPO receptor agonist for the treatment of ITP. Romiplostim, which was approved by the FDA in August 2008 and listed in the United States, is mainly used in patients who are ineffective or intolerant of corticosteroids, immunoglobulins, and splenectomy[13,14]. Because of the relatively little use in China, there are few clinical studies and related studies on the treatment of ITP by romiplostim. Our research collected relevant randomized controlled trials, used Cochrane system evaluation method, selection efficiency, and adverse reaction rate was Meta-analysis, in order to provide references for the clinical application of romiplostim.

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Materials and Methods

Inclusion and Exclusion Criteria

Pediatric patients who undergone spleen resection or not were included in this study. In addition, this factor has been taken into account when the analysis was performed.

Research type: All randomized controlled trials of the treatment of ITP in the romiplostim were evaluated.

Study Object: ITP patients younger than 18 years of age. Nationality, race and sex were not limited.

Intervention: Comparison with placebo.

Observation: Efficiency, occurrence of adverse events and occurrence of bleeding events.

Exclusion criteria: a. Data that have been included in other publications; b. Reported cases which were less than 5; c. Non-clinical research and non-treatment literature; d. Data incomplete and with no conclusions.

Methods

Database

We searched on PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, CBM (China Biology Medicine disc), CNKI (www.cnki.net), Wanfang (www.wanfangdata.com.cn), VIP (www.cqvip.com), and obtained references of randomized controlled trial of ITP for children with treatment of romiplostim with no limitation of languages (the search date was until 18 of January, 2017).

Reference Screening

All references were screened independently by 2 researchers. Case reports, reviews, systematic reviews, and repetitive literature were firstly excluded, Secondly, the titles and abstracts were screened; then, the full-text was analyzed in order to determine the availability.

Quality Evaluation

The methodological quality evaluation of the study was completed according to the quality evaluation method recommended by Cochrane collaboration. The main evaluation included: 1. random allocation method; 2. allocation concealment; 3. the blind method; 4. the integrity of the data; 5. other sources of bias.

Each evaluation project can be rated as low risk of bias, unclear risk of bias and high risk of bias, based on a specific evaluation criterion.

Data Extraction

Data extraction mainly included: 1. The basic situation of the test, baseline and disease status, follow-up time, loss of visits, and withdrawal of the two groups of patients; 2. The first author, the year, the drug and dose used in the trial, the total number of cases, and the endpoint (the number of cases available, the number of effective cases, the number of adverse events, the number of bleeding events, or the data obtained by calculation) of romiplostim and placebo. Two reviewers independently completed the related literature data extraction and cross-examination.

Statistical Analysis

We performed meta-analysis using RevMan 5.3 software (London, UK) provided by Cochrane collaboration. Counting data was carried out using relative risk (RR) and its 95% confidence interval; $p<0.05$ represented statistically significant difference. The references were investigated by I^2 heterogeneity analysis ($p= 0.1$ and $I^2 \leq 50\%$), which showed no statistical heterogeneity between studies using fixed-effect model. $p<0.1$ and $I^2> 50\%$ suggested the presence of significant heterogeneity among the studies by using a random effects model. Because of limited research and experimental data, funnel plot analysis and sensitivity analysis were not performed.

Results

Search Results

43 works were firstly investigated (Figure 1). 3 researches [15-17] of RCT were included in the inclusion criteria and then analyzed. All references searched were in English and published in full-text. A total of 3 trials, 102 patients were included in this system evaluation. Specific features of the clinical trials included were shown in Table I.

General Situation and Quality Evaluation

The sample sizes of the 3 trials[15-17] were the largest (62 cases) and smallest (18 cases). All 3 trials were randomized controlled trials. The 3 works only described the children as random groups, and did not describe the methods of generating random sequences in detail. The Elalfy et al[16] research was single blind. Tarantino et al[17] used the allocation concealment, and the Bussel et al[15] work was double-blind. There were no data missing, no alternative reporting results and other bias about these 3 researches[15-17]. Therefore, they were considered as low risk of bias.

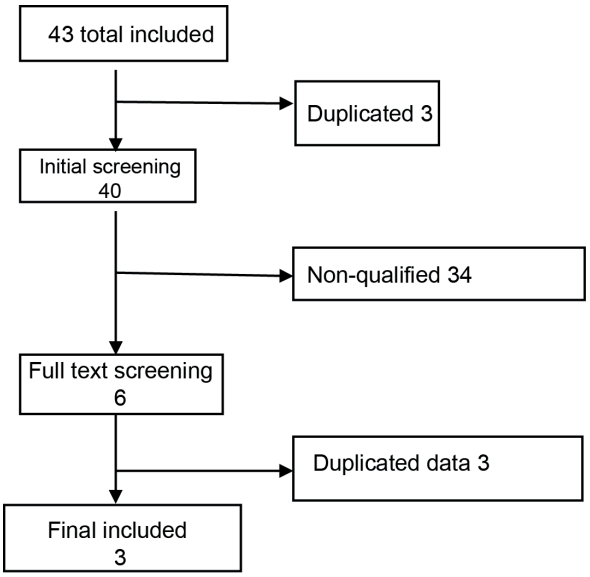

Figure 1. Reference screening process.

Intervention

In Bussel et al[15] study, according to age, the patients were divided into 3 groups with the ratio of 1:2:2 (Table II). The 3 groups were 12 months to 3 years' group, 3 to 12 years old and 12 years old to 18 years old, respectively. All groups were randomly assigned to the 3:1 ratio of romiplostim group and placebo group. To achieve the goal, platelet counts ranged from 50-250x10^9/l, and the range of drug doses studied ranged from 1 to 10 ug/Kg. When the platelet count was less than 50x10^9/l for 2 weeks, the 2 ug/kg dose was increased every two weeks. When the platelet count was between 50-250x10^9/l, the original dose was remained. When the platelet count ranged from 250-400x10^9/l for two weeks, the dose was reduced by 1 ug/kg. When the platelet count was greater than 400x10^9/l, the next planned dose was reduced by 1 ug/kg until the platelet count was less than 250x10^9/l.

In Elalfy et al[16] work, 18 patients were randomized to receive a 12-week course of romiplostim and placebo treatment with a ratio of 2:1. The initial dose was 1 ug/kg, which was gradually increased and maintained to 5 ug/kg.

In Tarantino et al[17] analysis, patients were divided into 3 groups according to age, from 1 to 6 years old, from 6 to 12 years, and from 12 to 18 years old. They were randomly assigned to receive treatment with romiplostim and a placebo at a ratio of 2:1 for 24 weeks. According to the target platelet count (50-200x109/l), the weekly adjusted dose range was 1-10 ug/kg.

Results of Meta-Analysis

Effective Rate

The 3 researches[15-17] reported the effective rate of the romiplostim treatment on ITP, a total of 102 cases. There were 71 cases in the Luo Ting Group and 31 cases in the placebo group. There was no heterogeneity among the studies (p=0.55, I^2=0%), and fixed effect model was used. Meta-analysis showed the total effective rate was 77.46% in the romiplostim group, and 12.9% in the placebo group. The difference was statistically significant (RR= 5.05, 95% CI (2.21, 11.53), p<0.01) (Figure 2). The results suggested that ITP has a high overall response rate in the treatment of romiplostim.

Table I. General data.

General Info References	Research Type	Age C/T	Sex (m/f) C/T	Case no. C/T	ITP C/T	Platelet baseline
Bussel et al[15]	RCT	2.5-16	16/6	17/5	2.2 y (1.5-3.7)	< 30
Elalfy et al[16]	RCT	1-18	13/5	12/6	2.3 y (1.2-7)	< 30
Tarantino et al[17]	RCT	1-17	27/35	42/20	1.9 y (0.8-14)	< 30

Note: C/T, Experimental /Control, C: Romiplostim group, T: Placebo control.

Table II. Intervention.

Reference	N		Intervention		Course
	Romiplostim	Control	Romiplostim	Control	
Bussel et al[15]	17	5	1-10 ug/kg	Placebo	12 weeks
Elalfy et al[16]	12	6	1-5 ug/kg	Placebo	12 weeks
Tarantino et al[17]	42	20	1-10 ug/kg	Placebo	24 weeks

Note: C/T, Experimental /Control, C: Romiplostim group, T: Placebo control.

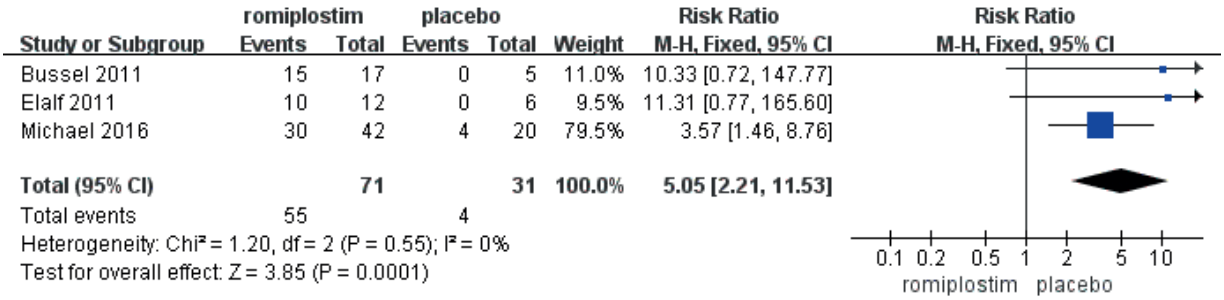

Figure 2. The effectiveness rate of Romiplostim on ITP.

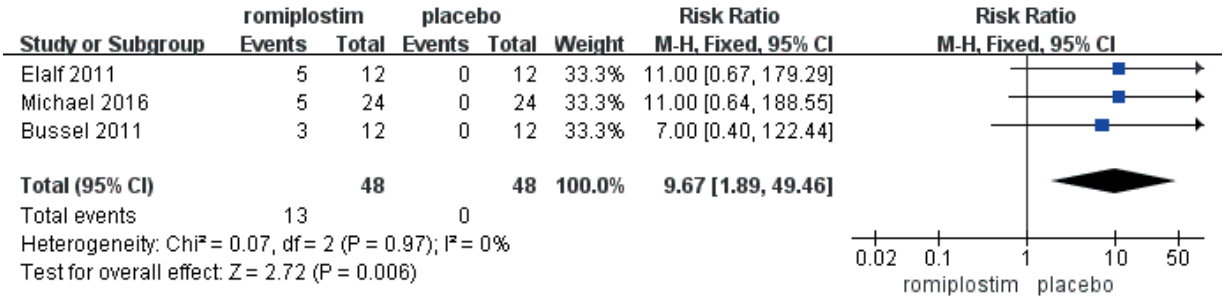

Figure 3. The average time of the rise of platelets to the standard of reaction of Romiplostim on ITP.

The Average Time of the Rise of Platelets to the Standard of Reaction

3 studies[15-17] reported the average weeks of romiplostim platelet rise to the response standard (50-200x109/L) for ITP, of which the romiplostim group was 3, 5, 5 weeks respectively, and the placebo group did not meet the response standard. There was no heterogeneity among the studies (p = 0.97, I^2 = 0%), and the fixed effect model was used. Meta-analysis showed that the average of romiplostim group was 4.5 weeks, and the placebo group did not reach the standard of reaction. The difference was statistically significant [RR=9.67, 95% CI (1.89, 49.46), p<0.01] (Figure 3) and indicated that romiplostim could significantly improve platelet count in patients with ITP.

Adverse Reaction

Most of the adverse effects during the treatment of romiplostim on ITP were mild. The main clinical manifestations included: epistaxis, headache, cough, nausea and vomiting, fatigue, bleeding, petechiae, rash, fever, throat pain and other less adverse reactions i.e. limb pain, back pain, abdominal pain, etc. (Table III). The occurrence of adverse events was reported in the 3 works[15-17], a total of 102 cases. There were 71 cases in the experimental group (romiplostim) and 31 cases in

Table III. Adverse response of Romiplostim on ITP.

Authors	Publishing time	Adverse responses	Severe Adverse responses
Bussel et al[15]	2011	Headache, epistaxis, cough, vomiting, skin flushing etc. to the head trauma	Lose consciousness
Elalfy et al[16]	2011	Headache (35%), epistaxis (35%), oropharyngeal pain (24%), fever (24%), contusion (18%), upper abdominal pain (18%), etc.	Sepsis
Tarantino et al[17]	2016	Contusion (50%), epistaxis (48%), headache (43%), etc.	Severe headache

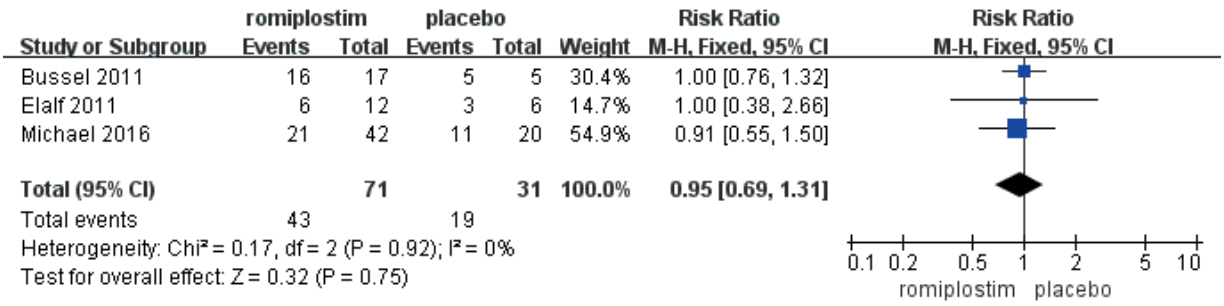

Figure 4. Adverse event occurrence rate of Romiplostim on ITP.

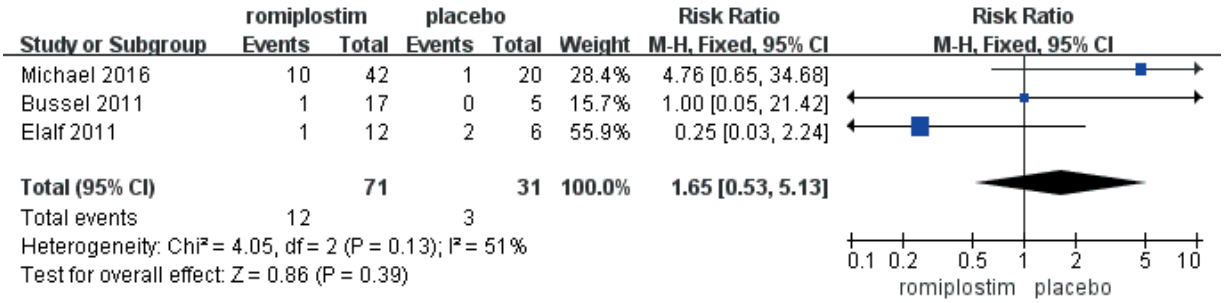

Figure 5. Occurrence of severe adverse reactions rate of Romiplostim on ITP.

the control group (Placebo). There was no heterogeneity among the studies (p=0.39, I^2=0%), and fixed effect model was used. Meta-analysis results showed that the occurrence of adverse reactions in the experimental group was 60.56%, compared with 61.29% in the placebo group, and there was no significant difference between the two groups (RR=0.95, 95% CI (0.69, 1.31), p>0.05) (Figure 4). This suggested that whether the clinical use of romiplostim would affect the occurrence of adverse events cannot be confirmed.

Occurrence of Severe Adverse Reactions

The occurrence of serious adverse reactions was reported[15-17], a total of 15 cases. There were 12 cases in the experimental group and 3 in the control group. The major adverse reactions included severe headache, epistaxis, contusion, and ecchymosis. The heterogeneity (p=0.39, I^2=51%) in each study, and the random effect model, were used. Meta-analysis showed that the occurrence of severe adverse reactions in the experimental group was 16.9% (12/71) and 9.6% in the placebo group (3/31), and the difference was not statistically significant [RR=1.65, 95% CI (0.53,5.31), p>0.05] (Figure 5). It is not clear whether the clinical use of romiplostim can affect the occurrence of serious adverse reactions.

Occurrence Rate of Hemorrhage Events

There were 2 works [15,17] reporting the occurrence of hemorrhage, a total of 84 cases. There were 59 cases in the experimental group and 25 cases in the control group. There was no heterogeneity among the studies (p=0.48, I^2=0%), and the fixed effect model was used. Meta-analysis showed that the hemorrhage rate in the experimental group was 79.66%, compared with 64% in the placebo group, and the difference was not statistically significant (RR=1.27, 95% CI (0.92, 1.75), p>0.05) (Figure 6). Whether the clinical use of romiplostim would affect the occurrence of hemorrhage events cannot be confirmed.

Discussion

Immune thrombocytopenia (ITP) is an autoimmune disease in children and adults characterized by accelerated platelet destruction and reduced platelet production[18,19]. Therefore, the development of platelet stimulatory therapy is promoted. Romiplostim[20], for example, as a thrombopoietin receptor agonist, is a Fc fusion protein (also known as antibody)[21]. Romiplostim increases the platelet production, which is similar to that of eTPO[22]. The mechanism is combined with the

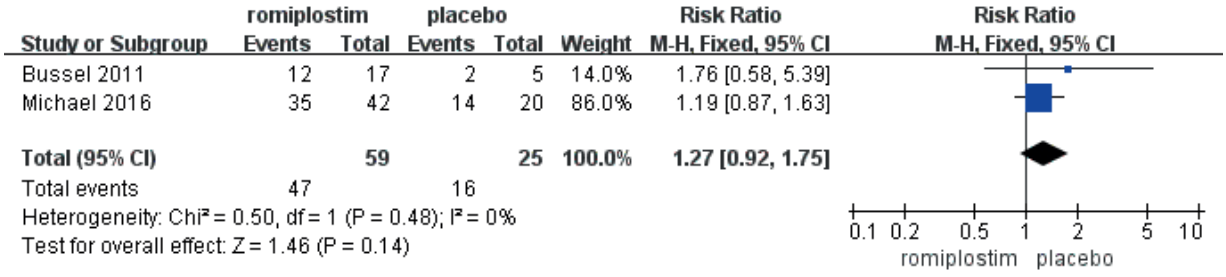

Figure 6. Hemorrhage event occurrence rate of Romiplostim on ITP.

extracellular domain of c-Mpl, induced by JAK-STAT, MARK, PI3K-AKT signal pathway. The proliferation of megakaryocyte promotes the maturation, inhibits their apoptosis, and increases platelet count[23,24]. Since there is no sequence of amino acid source with endogenous TPO, the possibility of inducing an antibody to cross-react with endogenous TPO is effectively decreased[24-26]. As a result, the romiplostim treatment of ITP has become a new option. 3 RCT works were included in this study (102 cases). The meta-analysis showed that the total effective rate was 77.46% (55/71) in romiplostim group, and in the placebo group was 12.9% (3/31), the difference was statistically significant (RR=5.05, 95% CI (2.21, 11.53), $p<0.01$). In the study of Bussel et al[27], the effective rate was 88.3% (15/17), in placebo group was 0 (0/5). In the course of treatment, the platelet count of patients was 50x109/l, average of 7 weeks (0-11 weeks) in romiplostim group, while the placebo group did not reach the standard reaction. In the Elalfy et al[16] study, the effective rate was 83.3% (10/12), 0 (0/6) in placebo. In the first week of the treatment process, romiplostim group platelet count increased significantly. After 5 weeks, the platelet count reached the peak value of 73.5x109/l (28-180), placebo group did not reach the standard reaction. In Tarantino et al study[17], the effective rate in romiplostim group was 71.4% (30/42), the placebo group was 20% (4/20). Romiplostim group sustained platelet response was 52% (22/42), 10% in the placebo group (2/20), which reached the standard of platelet reactivity. The average time for the romiplostim group was 4.5 weeks, compared with 20 weeks for the placebo group, which was in line with the efficiency of ITP treatment in adults (76%, 87%, 83%, 80%, respectively)[27-29]. The major adverse reactions for romiplostim in the treatment for ITP patients are: headache, epistaxis, contusion, vomiting, skin flushing, petechiae, fever, upper abdominal pain, etc. Other patients suffered from joint pain, anxiety and back pain during the study period. There were 12 severe adverse events (11.7%), which mainly occurred in the study of Tarantino et al[17] (10 cases). The main reactions were nasal bleeding, bruising, headache, bronchitis, nausea, ecchymosis, epilepsy, fever, thrombocytosis, urinary tract infection, vomiting etc. Only headache and thrombocytosis occurring in the same patient were considered treatment-correlated. Comparing the romiplostim used in the included studies with a long-term study of adult patients for the treatment of ITP (29), the adverse occurrence rate was 60.56% (43/71) lower than 94% (135/143) in adults, and there was no increase in bone marrow reticulum protein and thrombosis events. The hemorrhage events mainly manifested as skin petechia, ecchymosis, no life-threatening intracranial hemorrhage. In comparison with the placebo group, the difference of occurrence of adverse events and the occurrence of bleeding events, compared with the placebo group, was not statistically significant. Although there were many adverse reactions of romiplostim, most of them were evaluated as mild to moderate adverse events, which did not affect the treatment and were very fewer severe adverse events associated with the drug. Therefore, romiplostim was considered as highly clinical safe.

Conclusions

Romiplostim has a high rate of response in the clinical treatment of ITP in pediatric patients. Due to the absence of sequence homology with the endogenous TPO, the adverse reactions were mild and well tolerated, then, it can be considered a new option for the clinical treatment of ITP patients.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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