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ORIGINAL ARTICLE

Romiplostim in children with chronic refractory ITP: randomized placebo controlled study

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Abstract Romiplostim stimulates thrombopoietin receptor to increase platelet production of megakaryocytes in idiopathic thrombocytopenic purpura (ITP). This study aimed to evaluate the safety and efficacy of romiplostim in children with chronic ITP. Eighteen patients with chronic ITP, either none responsive or failed to maintain response on two or more therapeutic modalities, were enrolled. Patients were randomized (2:1) to receive romiplostim or placebo for 12 weeks, initiated at 1 μg/kg/week, escalated to 5 μg/kg/week, and then tapered. Median patients' age was 8.5 years, and the median baseline platelet count (PC) was 10.5×10^9/L. The median weekly dose of romiplostim was 2 μg/kg. Fifty percent of patients in both romiplostim and placebo arms had at least one adverse event (AE); none was serious. Ten patients on romiplostim (83.3%) maintained the efficacy endpoint (PC>50,000). Romiplostim was well-tolerated and efficient in treating the children with chronic refractory ITP with no unexpected AEs.

Keywords Chronic ITP · Pediatrics · Romiplostim

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Abbreviations

ITP	Immune thrombocytopenia
PC	Platelet count
AE	Adverse event

Introduction

Recent research on the pathogenesis of ITP points to a role of suboptimal platelet production [1], which supported the development of new treatment options of thrombopoiesis-stimulating agent, such as Thrombopoietin (TPO) agonist, romiplostim [2]. Clinical trials have shown that romiplostim increases platelet counts in adult patients with chronic ITP [3]. Potential adverse effects of romiplostim include thrombocytosis, thrombosis, rebound worsening of thrombocytopenia, and increase in bone marrow reticulin [4]. In this pilot study, we aimed to assess the success of treating patients with chronic resistant ITP with the new therapy; romiplostim compared with a placebo and whether they develop any adverse drug reaction or they need to add rescue treatment.

Design and methods

This randomized single-blinded placebo-controlled trial was carried out at a single institution of Ain Shams University in the period from March to July 2010 on patients diagnosed with ITP (isolated thrombocytopenia) according to American Society of Hematology guidelines [5]. It included 18 non-splenectomized patients with chronic ITP (persistent thrombocytopenia >12 months after diagnosis) [6]. They were either non-responder or failed to

maintain response to at least two treatment modalities before enrollment; 5 females and 13 males. Their ages ranged from 2.5 to 6 years of age with disease duration ranged from >1 to 7 years and basal PC <20,000/mm^3. All the patients discontinued any medication 2 weeks prior to study entry. Exclusion criteria were history or evidence of a bone marrow disorder or serious bleeding (life-threatening bleedings). Data of ITP patients included demographic data, disease onset, course and duration, treatment modalities used, and their response according to the definition of Rodeghiero et al. [6]. The severity of bleeding was evaluated using criteria of Buchanan and Adix [7]. Investigation included, complete blood count (CBC) done at the study entry and revised weekly for up to15 weeks. Bone marrow (BM) aspirate and trephine were done initially and at week 18 to assess any BM changes related to romiplostim treatment. Rescue treatment (IVIG 2 g/kg) will be given in case of serious bleeding or head trauma with loss of consciousness

Statistical analysis

Data were analyzed using SPSS (v. 17.0, Echosoft Corp., USA, 2008). Data were expressed as median and range for quantitative measures and both number and percentage for categorized data. Wilcoxon signed-rank test and the Mann–Whitney test were used for nonparametric data. Fisher's exact test was used for categorized data. Ranked Spearman correlation test was used for possible association between each two variables.

Results

Table 1 characterizes the group of patients on romiplostim and placebo. All patients completed the study. Six of 12 patients in the romiplostim arm (50%) and 3 of 6 in the placebo arm (50%) had at least one adverse event (AE) during the treatment period. The most common reported AEs were headache, epistaxis, cough, and vomiting (8% and 16% among romiplostim and placebo group, respectively), while skin rash was reported in 16% of patients on romiplostim. No patients died during the study. Prior to study entry, all patients had received steroids during the course of their disease, while 44% received the three therapeutic modalities (steroid, IVIG and anti D) in combination or alternatively, and 22% received cytotoxic drugs or immune-modulator agents. All these treatment modalities were discontinued 2 weeks prior to study entry.

A significant increase of PC from the baseline PC was observed among the romiplostim group within 1 week of the first dose (1 μg/kg) of treatment (p=0.039) and continued for 15 weeks (p=0.001). Eleven (91.67%) patients reached the target range (>50×10^9/L) by the fifth week (5 ug/kg), while 10 patients (83.3%) on romiplostim achieved the efficacy endpoint compared to none on the placebo. None of our patients experienced thrombocytosis or rebound thrombocytopenia. None of the patients in the romiplostim arm developed BM fibrosis by week 18 of follow up.

In the romiplostim arm, the peak PC was reached by the fifth week of treatment (5 μg/kg) (Fig. 1). Six patients (50%) on romiplostim arm maintained the response 3 weeks after drug discontinuation. The changes in PC among romiplostim group of patients were dose-dependent (Fig. 2).

Rescue medication (IVIG 1 g/kg for two doses) was administered to 1 of 12 (8.3%) of the romiplostim group (due to head trauma with loss of consciousness) and 2 of 6 (33.3%) of the placebo-treated patients because of serious bleeding during the 12-week treatment period with no interruption of romiplostim or the placebo.

During the study period, patients on the romiplostim arm showed decreased bleeding severity for those with bleeding grade 3 prior to study from 33.3% to 0% and for those with grade 2 from 50% to 16.6% (p=0.002).

Table 1 Characteristics of romiplostim and placebo-treated patients

	Romiplostim group (N=12)	Placebo group (N=6)	p value*
Age (years)	9.5 (2.5–16)	7(4–15)	0.750
Sex (n, %)			
Females	2 (16.7%)	3 (50%)	0.286**
Males	10 (83.3%)	3 (50%)	
Disease duration (years) (median & range)	2.3 (1.2–7.0)	3.0 (1.5–6.5)	0.494
Baseline PC (x 10^9/L) (median & range)	10.5(2–20)	10.5(6–20)	0.750
Peak PC (x 10^9/L) (median & range)	73.5(28–180)	28.5(17–51)	0.001
PC 3 weeks after treatment (median & range)	47.5(24–92)	19 (14–32)	0.001

*p value for Mann–Whitney test,**p value for Fisher's exact test

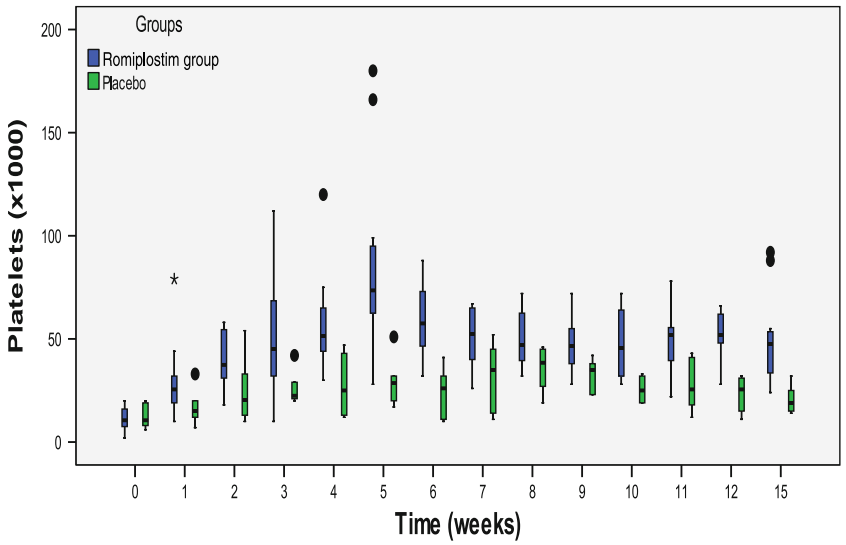

Fig. 1 Boxplots of medians, interquartile ranges, and the outliers (*dot,* outliers; *asterisk,* extreme outliers) of platelet counts all through the study period and 3 weeks later in romiplostim and placebo groups

Discussion

ITP is a heterogeneous disorder concerning natural history [8] and pattern of treatment response [9]. The risk of bleeding depends on bleeding signs and platelet level [10]. The novel thrombopoietin agonist romiplostim was used in this study. In the report by Buchanan et al.; 88.2% of children with chronic refractory ITP in the romiplostim-treated arm achieved the efficacy endpoints during the treatment period compared to none of the placebo [11]. In the present study, 83.3% of patients in the romiplostim and none in the placebo treated arm achieved the efficacy endpoint, while other studies on adults with ITP reported response rates of 75%, 87%, 83% and 80%, respectively [12–15].

A significant increase of PC was observed in our patients on romiplostim within 1 week after the first dose, and 91.67% of patients on romiplostim reached the target range by the fifth week (5 μg/kg). None of our patients experienced limiting adverse effects as thrombocytosis. In adults with chronic ITP similar response to romiplostim occurred by the first assessment on day 8, and two of their patients exceeded the target range ($>450\times10^9$/L) [12]. In another study, platelet increased within 1–2 weeks of romiplostim treatment, and 50% of patients achieved the target PC within 2–3 weeks of treatment [14]. Recently, Meletis et al. reported a three-fold increase in PC within 7 days following the first dose of romiplostim [16]. Fifty percent of our patients in both romiplostim and placebo arms experienced at least one mild AE, which reflects similar results in adults with ITP [14], and Buchanan et al. reported no additional safety concerns observed in their study as compared to adults with chronic ITP [11]. Long-term treatment with romiplostim for up to 156 weeks was effective and apparently safe [13].

Rescue medication was administered to 8.3% and 33.3% of our patients on romiplostim and placebo, respectively. Similar results were reported in adults with overall 60% of patients in the placebo group who received rescue medication compared to 22% of patients in the romiplostim group [14].

Patients in the romiplostim arm showed a significant decrease in bleeding severity during the treatment ($p=0.002$). This is in agreement with the studies in adults with chronic ITP [17, 18]. After stopping romiplostim in nine studies on adult patients with ITP; four events of recurrence of thrombocytopenia occurred; however, 50% of our patients on romiplostim maintained platelet response after 3 weeks of drug discontinuation, and no rebound thrombocytopenia was reported. Impema et al. reported that effects of romiplostim on platelets were transient at a dosage up to 17 μg/kg/wk [4].

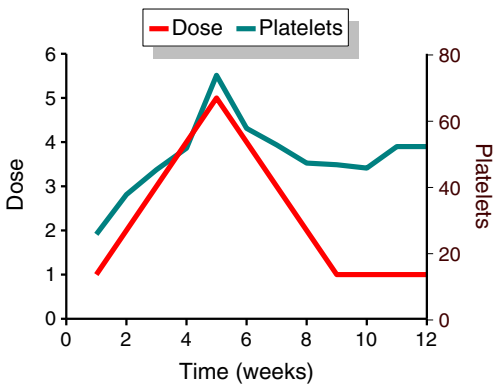

Fig. 2 Correlation between dose of romiplostim and platelet count all through the study period (12 weeks)

Conclusion

In pediatric patients with chronic refractory ITP, romiplostim was well-tolerated and showed platelet increase with neither serious AEs nor serious bleedings in this short-term (15 weeks) prospective romiplostim placebo-controlled study. Studies on the long-term use of this drug are warranted.

Conflict of interest The authors declare no conflicts of interest to be disclosed.

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