Journal of Vessels and Circulation
Qom University of Medical Sciences

Summer 2023. Volume 4. Number 3

Research Paper

Efficacy and Complications of Romiplostim Versus Rituximab in Pediatric Immune Thrombocytopenic Purpura

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Please cite this article as Felahati V, Noori S, Dorreh F, Noori A, Atarod MH. Efficacy and Complications of Romiplostim Versus Rituximab in Pediatric Immune Thrombocytopenic Purpura. J Vessel Circ. 2023; 4(3):101-108. http://dx.doi.org/10.32598/JVC.4.3.31.35

http://dx.doi.org/10.32598/JVC.4.3.31.35

Article info:
Received: 20 Mar 2023
Accepted: 28 May 2023
Publish: 01 Jul 2023

Keywords:
Romiplostim, Rituximab, Side effects, Platelets

ABSTRACT

Background and Aim: Idiopathic thrombocytopenic purpura (ITP) is a chronic autoimmune disease characterized by persistent thrombocytopenia and mucocutaneous bleeding. The aim of this study was to evaluate the effects and side effects of rituximab and romiplostim in children with ITP.

Materials and Methods: The present prospective cohort was conducted on children with ITP who met the inclusion criteria. Romiplostim and rituximab were prescribed for these children by the physician. For each child, follow-up for side effects and the effectiveness of the medication continued for six months. The criterion for treatment response in patients was an increase in the platelet count of >30,000 per cubic millimeter of peripheral blood. To evaluate the possible side effects of the drugs, patients were evaluated monthly for fever, skin rashes, respiratory infections, and peripheral edema. Finally, the data obtained from the patients were statistically analyzed using SPSS software, version 26.

Results: In the current study, 140 children were included and divided into the rituximab and romiplostim groups consisting of 70 children. The average age of the children participating in the study ranged from 8 to 9 years. There was no significant difference between the two study groups in terms of age. Changes in the average platelet count during the nine measurement periods were significantly higher in the romiplostim group compared to the rituximab group ($P<0.001$). In addition, the treatment response rate was significantly higher in the romiplostim group than in the rituximab group (71.4% vs. 48.6%, respectively; $P=0.006$). None of the children taking two drugs experienced peripheral edema. Regarding the examination of other side effects related to the use of these two drugs, it should be noted that the rates of fever, skin rashes, and respiratory infections, although there was no significant difference between the two study groups during the nine repeated measurements ($P>0.05$), were generally lower in the romiplostim group than in the rituximab group during the second to fourth weeks of the study.

Conclusion: Romiplostim demonstrates better performance than rituximab in increasing the number of peripheral blood platelets in children with immune thrombocytopenia purpura, and the response rate to treatment is also higher with romiplostim compared to rituximab. Additionally, Romiplostim is associated with fewer complications.

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is a chronic autoimmune disease characterized by persistent thrombocytopenia and mucocutaneous bleeding [1]. This disorder is one of the common causes of thrombocytopenia (defined as a platelet count of <100,000 per milliliter) in children, especially in the age range of 2-5 years, and in children, and it mainly occurs following viral infections [2, 3]. In more than 80% of cases, ITP improves spontaneously within one to two months. However, thrombocytopenia can become chronic in a subset of patients who require extensive treatment. The spectrum of clinical manifestations of this disease is diverse, ranging from mild and asymptomatic thrombocytopenia to severe cases (characterized by petechiae and purpura), with patients at high risk for acute mucosal, digestive system, and intracranial bleeding [4-7]. In this disease, the immune system produces autoantibodies against platelet glycoproteins, mainly targeting glycoprotein IIb/IIIa and, less frequently, glycoproteins Ib/IX, Ia, and IIa, leading to their destruction in the reticuloendothelial system [8, 9].

Recent evidence shows that ITP is not only an autoantibody-mediated platelet destruction disease but also disrupts platelet production in the bone marrow [10]. Reduced platelet production has been linked to the direct effects of autoantibodies on megakaryocytes. This occurs in patients with disorders that result in a decrease in thrombopoietin (TPO), leading to thrombocytopenia [6, 11, 12]. Currently, the treatment for patients with ITP focuses on inducing an early increase in platelet count through the administration of steroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin [13, 14]. Alternatively, long-term maintenance of platelet levels can be achieved through splenectomy or the use of drugs, such as rituximab, danazol, azathioprine, or even long-term corticosteroid therapy [15, 16]. These treatments have been effective for a large number of patients, but they are associated with issues related to the duration of treatment response and the occurrence of side effects. Currently, available treatments lead to an increase in platelet count in patients with ITP by reducing platelet destruction.

Romiplostim is a thrombopoietic agent that, in recent studies, has been shown to increase the number of platelets not only in healthy people [17, 18] but also in patients with ITP. Romiplostim is a unique thrombopoiesis-stimulating protein composed of two IgG Fc units with four copies of a TPO mimetic peptide, which results in an increase in platelet production through a mechanism similar to endogenous TPOs [19]. However, it does not share any amino acid sequence similarity with TPO [20]. Based on the available evidence, the administration of a single dose of 1-10 µg/kg romiplostim in patients with ITP leads to an increase in the number of platelets by 50,000 or more, which is typically observed. This increase decreases to <50,000 within 15 days [20, 21]. In addition, the weekly administration of romiplostim leads to an increase and maintenance of the platelet levels after six weeks from the start of treatment [20].

Considering that there is no specific guideline for the treatment of chronic ITP in children, and despite the availability of many drugs in this area, finding a medication with higher effectiveness and fewer side effects for these patients is of great importance. Therefore, considering that some recent reports have indicated the effective role of romiplostim in ITP, and considering the limited information in this field, this research aimed to examine the efficacy of romiplostim and rituximab in pediatric patients with chronic immune thrombocytopenic purpura who are being treated at Amir Kabir Hospital in Arak.

Materials and Methods

The current prospective cohort study was conducted with a six-month follow-up. After obtaining approval and receiving the code of ethics from the Ethics Committee of Arak University of Medical Sciences, and registering this observational study with parallel groups as a census over a period of six months, it was conducted on all children aged 5-15 years with chronic ITP at the Amirkabir Hospital in Arak City.

The inclusion criteria were the presence of hemoglobin levels >10 g/dL, absence of kidney failure, a negative Coombs test, absence of infectious diseases, malignancy, potential autoimmune diseases associated with ITP, and absence of safety defects, while the exclusion criteria included patients who experienced severe complications and those who abandoned follow-up for treatment.

The sample size was calculated using the results of a similar study [22] and considering a 25% difference at a confidence level of 95% with a power of 80% by Stata software, version 11. This calculation resulted in 70 individuals in each group. After reviewing and evaluating the case files, these children were divided into two identical groups and treated with injectable romiplostim at a dose of 1 mcg/kg (subcutaneous, AMGEN company) and injectable rituximab at a dose of 375 mg/m^2 (AC-

TOVERCO company). It should be noted that these drugs were prescribed based on the doctor's judgment and according to the patient's condition in a completely routine manner. The researcher had no role in this part of the study. The initial diagnosis of ITP was based on the initial state of the disease, the absence of hepatomegaly and splenomegaly, negative serological tests for hepatitis B and C, and HIV, as well as a negative result from bone marrow aspiration. After obtaining informed consent from the parents of the patients, the demographic information of the patients was recorded, and the patients in both groups were examined. The criterion for treatment response in patients was an increase in platelet count. Platelet counts were measured at the beginning of the study, during the first to fourth weeks, and then monthly after the start of treatment, and these results were recorded in the prepared checklist.

Treatment response criteria were measured according to the International Working Group (IWG) ITP criteria, where the baseline platelet level for patients with ITP was considered to be $<30\times10^9$ L.

1. Complete answer: Platelet count $\geq100\times10^9$/L

2. Relative response: Platelet count $\geq30\times10^9$/L

3. No response: Platelet count $<30\times10^9$/L

At the beginning of the study, patients who were treated with corticosteroids after tapering or stopping IVIG were subjected to the possible treatments used in this study. Corticosteroids, IVIG, and splenectomy were also considered alternative treatments for people who did not respond to the provided therapies. To evaluate possible side effects of the drugs, patients were assessed monthly for fever, skin rashes, respiratory infections, and peripheral edema. To evaluate possible side effects of drugs, patients were assessed monthly for fever, rash, respiratory infections, and peripheral edema. To evaluate the possible side effects of the drugs, patients were assessed monthly for fever, skin rashes, respiratory infections, and peripheral edema. Parents were educated about the possible side effects of the treatments and instructed to contact the plan administrators in case of any complications.

Data were analyzed by SPSS software, version 26, using repeated measures analysis of variance for quantitative data and the GEE method for qualitative data. Descriptive statistics were presented in the form of tables and graphs showing means and percentages.

Results

In the romiplostim group, 29(41.1%) girls and 41(58.6%) boys were examined, while the Rituximab group included 33(47.1%) girls and 37(52.9%) boys. The mean age of the children in the romiplostim group was 8.8±1.83 years, while in the rituximab group, it was 8.71±1.9 years. The romiplostim group showed a significant improvement and increase in peripheral blood platelets compared to the rituximab group over nine measurements. Although the incidence of fever in the studied children was lower in the romiplostim group compared to the rituximab group, these differences were not significant across the nine measurement points. There was no statistically significant difference in the presence of skin rashes and respiratory infections between the two groups during the measurement period. None of the participating children in either group exhibited peripheral edema during the nine measurement and examination sessions. Table 1 presents the descriptive characteristics of the treatment response in the two study groups. The rate of complete response to treatment was significantly better in the romiplastim group than in the rituximab group (P=0.006) (Table 2).

Discussion

ITP is an autoimmune disorder characterized by low platelet counts, purpura, and hemorrhagic episodes caused by antiplatelet autoantibodies. This disease is a type of chronic complication in children. The most serious complication of ITP is bleeding, particularly the rare but potentially fatal complication of intracranial hemorrhage. Therefore, it is crucial to employ a therapeutic combination that can effectively suppress this disease and increase the number of peripheral blood platelets in these children. Different types of recombinant drugs have been used in this context, such as rituximab and romiplostim. Examining the side effects and efficacy of these drugs can greatly aid in the treatment of this disease and enhance our understanding of their use. In the current study, the average age of the children participating was between 8 and 9 years, and there was no significant difference in age between the two study groups. Regarding the gender prevalence of this disease, it should be noted that the incidence of acute ITP is equal in boys and girls between the ages of 1 and 7 [23]. The adult form of this disease tends to become chronic and is more common in women [24]. Some studies have indicated that the prevalence of this disease is higher in children, particularly in the age group of 2 to 5 years old [1].

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Table 1. Comparison of clinical findings between the two treatment groups

Variables			Mean±SD/No. (%)		P
			Romiplostim	Rituximab	
Platelet count (cells/µL)	1 week		31.06±16.02	112. 51±39.85	<0.001
	2 weeks		125.07±44.29	27.73±8.57	
	3 weeks		124.73±56.47	83.43±29.28	
	4 weeks		141.57±67.56	95.53±38.14	
	2 months		152.33±76.04	101.3±51	
	3 months		157.5±84.57	107.64±60.64	
	4 months		159.6±86.02	110.39±51	
	5 months		161.37±88.27	107.06±60.64	
	6 months		125.07±8.57	106.17±64.23	
Fever	1 week	Yes	3(4.3)	7(10)	0.946
		No	67(95.7)	63(90)	
	2 weeks	Yes	2(2.9)	4(7.5)	
		No	68(97.1)	66(94.3)	
	3 weeks	Yes	2(2.9)	4(7.5)	
		No	68(97.1)	66(94.3)	
	4 weeks	Yes	1(1.4)	2(2.9)	
		No	69(68.6)	68(97.1)	
	2 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	3 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	4 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	5 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	6 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	

Variables			Mean±SD/No. (%)		P
			Romiplostim	Rituximab	
Skin rashes	1 week	Yes	5(7.1)	10(14.3)	0.295
		No	65(92.2)	60(85.7)	
	2 week	Yes	4(7.5)	10(14.3)	
		No	66(94.3)	60(85.7)	
	3 weeks	Yes	3(4.3)	9(12.9)	
		No	67(95.7)	61(87.1)	
	4 weeks	Yes	1(1.4)	9(12.9)	
		No	69(98.6)	61(87.1)	
	2 months	Yes	0(0)	5(7.1)	
		No	70(100)	65(92.9)	
	3 months	Yes	0(0)	4(5.7)	
		No	70(100)	66(94.3)	
	4 months	Yes	0(0)	1(1.4)	
		No	70(100)	69(98.6)	
	5 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	6 month	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
Respiratory infection	1 week	Yes	3(4.3)	7(10)	0.956
		No	67(95.7)	63(90)	
	2 weeks	Yes	2(2.9)	5(7.1)	
		No	68(97.1)	65(92.1)	
	3 weeks	Yes	1(1.4)	3(4.3)	
		No	69(98.6)	67(95.7)	
	4 weeks	Yes	0(0)	3(4.3)	
		No	70(100)	67(95.7)	
	2 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	3 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	4 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	5 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	6 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	

Variables			Mean±SD/No. (%)		P
			Romiplostim	Rituximab	
Peripheral edema	1 week	Yes	0(0)	0(0)	1
		No	70(100)	70(100)	
	2 weeks	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	3 weeks	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	4 weeks	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	2 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	3 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	4 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	5 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	
	6 months	Yes	0(0)	0(0)	
		No	70(100)	70(100)	

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In comparing the two drugs, rituximab, and romiplostim, in terms of platelet improvement, it should be noted that the changes in platelet counts during the nine measurement points in the romiplostim group were significantly higher than those in the rituximab group. In other words, romiplostim caused a greater increase in platelet counts compared to rituximab. In addition, the rate of response to treatment was significantly higher in the romiplostim group than in the rituximab group. In general, it can be concluded that romiplestim performed better than rituximab in improving the platelet count of children with ITP during the study period. So far, a study that accurately compares the effects of these two drugs in this area has not been conducted thoroughly However, in a study comparing these two drugs, it was noted that patients who received romiplostim and rituximab were significantly less likely to require additional treatment. It may also effectively improve platelet counts in patients who experience frequent bleeding [25].

Table 2. Comparison of the frequency of response to treatment between the two treatment groups

Variable		No. (%)		P
		Romiplostim	Rituximab	
Response to treatment	Yes	50(71.4)	34(48.6)	0.006
	No	20(28.4)	36(51.4)	

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In a study comparing romiplostim with placebo, it was reported that romiplostim led to a significant increase in platelet counts (response to treatment) in 79% and 88% of patients with chronic ITP in the groups with and without a history of splenectomy, respectively, which is significantly higher than in the placebo group. No other side effects of the treatment with this drug have been reported, and no difference was found between patients receiving romiplostim and those receiving the placebo [26]. In addition, another study indicated that the response to treatment (mean platelet count >50,000) in patients receiving romiplostim was significantly 2.3 times higher than in patients treated with standard therapy. Moreover, patients undergoing treatment with romiplostim experienced a significantly lower rate of treatment failure compared to those receiving standard therapy (11% vs. 30%, respectively; P<0.0001). Patients treated with romiplostim also reported fewer side effects and higher quality of life. The prevalence of serious treatment-related adverse events in the romiplostim group was found to be 23%, compared to 37% in the standard treatment group [27].

In another study on peripheral edema associated with the use of romiplostim, it was noted that this complication is relatively uncommon, with <6% of users experiencing it in the distal extremities [28]. In the review of other side effects related to the use of these two drugs, it should be mentioned that the incidence of fever, skin rashes, and respiratory infections did not show a significant difference between the two study groups during the nine repeated measurements. However, these side effects typically occurred in the second to fourth weeks of the study. These symptoms may be due to the child being exposed to other infectious diseases or having underlying conditions. It would be advisable to conduct further studies in the form of clinical trials in this area. Regarding complications associated with Romiplostim, as mentioned earlier, two separate studies conducted by Kuter et al. confirmed the absence of severe complications and respiratory diseases in patients [26, 27]. The occurrence of skin rashes associated with the use of romiplostim can depend on the dose of the drug. One study stated that skin rashes are a side effect of treatment with romiplostim at higher doses (750 µg), but they are not reported at the 500 µg dose This report also describes a successful rechallenge of romiplostim after the resolution of the rash [29, 30]. One of the rare side effects associated with the use of rituximab is the occurrence of serum sickness syndrome. According to a study, the two most common symptoms are fever and skin rashes. It has been reported that serum sickness is a much rarer side effect characterized by fever, skin rashes, polyarthralgia or arthritis, proteinuria, hematuria, increased inflammatory markers, and decreased complement levels, which usually develop 10-14 days after treatment [31].

Conclusion

Romiplostim demonstrates better efficacy than rituximab in increasing the number of peripheral blood platelets in children with ITP, and the response rate to treatment is also higher with romiplostim compared to rituximab. Although skin rash and fever side effects were reported less frequently in the romiplostim group than in the rituximab group, the difference was not significant across multiple evaluations.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1400.046).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors are grateful to the Vice-Chancellor for Research and Technology of Arak University of Medical Sciences and the Vice Chancellor for Research at the School of Medicine.

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