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Efficacy and safety of romiplostim in adult Iraqi patients with refractory immune thrombocytopenia

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Abstract:

BACKGROUND: Immune thrombocytopenia (ITP) is an immune-mediated acquired disease characterized by decrease of the platelet count. The majority of adult patients progress to chronic stage with some of them failed to respond or relapsed after the second-line therapy. Romiplostim is a thrombopoietin receptor agonist recently approved for patients with chronic ITP, it was recently licensed and introduced for use in Iraq. The aim of this study was to assess the efficacy and safety of romiplostim among patients with refractory ITP.

PATIENTS AND METHODS: This prospective study was conducted between April 2017 and June 2018 in two hematology centers in Baghdad and Basra. A group of 56 adult patients with refractory ITP enrolled in this study. The patients were evaluated before the weekly scheduled romiplostim and followed for efficacy and safety of the treatment.

RESULTS: the median age was 39 years with a female-to-male ratio of 4:1. The response rate (platelet $\geq 50 \times 10^9$/l) was observed in 75% of the enrolled patient. The time to initial response was 2.5 weeks, and the mean dose of romiplostim used to achieve a sustained response was 3.1 mcg/kg. The response rate was significantly higher among splenectomized (94.4% vs. 65.8%). There was no difference in response regarding the age and gender. The most frequent adverse effects were joint pain (35.7%), followed by headache (32.1%) and fatigue (21.4%), resolved spontaneously within 2 days. Six patients developed thrombocytosis without any thrombotic event.

CONCLUSIONS: Romiplostim is an effective option among Iraqi patients with refractory ITP as a long-term treatment or as a bridge for another intervention, with a relatively safe toxicity profile.

Keyword:

Efficacy, immune thrombocytopenia, refractory, romiplostim, safety

Introduction

Immune thrombocytopenia (ITP) is an immune-mediated acquired disease characterized by transient or persistent decrease of the platelet count and depending upon the degree of thrombocytopenia, increased risk of bleeding.[1] The estimated incidence of ITP in adults is 33 per 1,000,000 per year, with women affected more than men at a rate of approximately 1.3:1.0–3.0:1.0.[2,3]

Acute ITP, a term originally used primarily for children, is now considered newly diagnosed occurring within the first 3 months postdiagnosis.[1,4] The majority of the adult patients will progress through a second termed-persistent phase to the chronic stage in which symptoms remain present beyond 12 months.[5] ITP is termed severe when it is characterized by the necessity of active intervention to treat bleeding symptoms.[1] The term "refractory" has been interpreted in different ways. For some it implies the

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postsplenectomy patient who has failed to respond or who has relapsed. While others interpret it to include those who do not respond well to treatment irrespective of splenectomy status.[1,6]

Bleeding symptoms in ITP patients typically present as either a mild form, such as bleeding in skin and mucosal regions, or a more severe, life-threatening form, such as bleeding in gastrointestinal or intracranial areas.[4,7] Patients with ITP have varying platelet counts as a result of the disease. Those with platelet counts above 50,000 per microliter rarely bleed, but below this value, there are large differences in clinical phenotypes between patients that are as of yet unexplained.[6,7] Therefore, the aim of therapeutic intervention is to reduce the likelihood of bleeding by slowing down the platelets destruction and maintaining an adequate platelet level.[8] Corticosteroids are the first-line therapy with or without intravenous immunoglobulin (IVIG) and anti-D. The second-line therapy includes immune suppressants, rituximab, splenectomy, and thrombopoietin receptor agonists.[6]

Romiplostim is a peptide domain that binds to the TPO receptor-stimulating megakaryopoiesis, and it was the first thrombopoietic agent developed for the treatment of ITP.[9] Although romiplostim has been approved and available in the United States since 2008 as a long-term treatment for chronic ITP in adults who have not responded to other treatments,[10] it was recently introduced for use and licensed in Iraq in 2017 in the reference hematology centers over the country.

The study aimed to assess the efficacy and safety of romiplostim in the clinical practice among a group of patients with refractory ITP treated in two main hematology centers in Iraq.

Patients and Methods

This was a prospective cohort study, conducted at Baghdad and Basra Hematology Centers from April 2017 to June 2018. The study enrolled a group of adult patients with refractory ITP, i.e., those who failed to respond after at least 2 lines of treatment, with or without splenectomy. The study including the protocol and intervention procedures was approved by the Medicine Ethical Committee of Iraqi Board for Medical Specialization and in accordance with the principles of the revised declaration of Helsinki. The protocol was to treat them with once weekly dose-escalated romiplostim by subcutaneous injection and followed them weekly for the response and if any adverse effects. Before treatment, an informed consent was obtained for each patient and all the patients were sent for chest X-ray abdominal ultrasound, antinuclear antibodies, ds-DNA, Coomb's test, hepatitis B surface antigen, hepatitis C virus, HIV antibodies, and bone marrow examination to exclude secondary ITP cases.

Inclusion criteria

All the patients older than 14 years with refractory ITP who met any of the following criteria, using the autoanalyzer:

1. Platelets count $<30 \times 10^9$/L
2. Platelets count $<50 \times 10^9$/L with a history of spontaneous bleeding, or the patient was in need for antiplatelet, anticoagulant, or major surgical intervention.

Exclusion criteria

1. Cases of secondary ITP
2. Patients who could not adhere properly to the schedule of treatment.

The response criteria of treatment was to reach a safe platelet count ($50–200 \times 10^9$/L) that sustained for at least 4 weeks without use of rescue medications, IVIG or anti-D, during the 4 weeks before each qualifying platelet count. Patients who succeed to reach this target we considered them "responders," while those who did not after 4 successive weeks of maximum dose (10 mcg/kg) were called "nonresponders."

Platelet count was checked weekly before the administration of romiplostim for dose adjustment according to the recommendations of the manufacturing company.[10]

Regarding safety, all the patients were evaluated weekly by history and complete blood counts and every 3 months to evaluate renal function tests, liver function tests and peripheral blood for morphology findings suggestive of bone marrow fibrosis. If so, then bone marrow examination would be requested for confirming or refuting.

Statistical analysis

IBM SPSS program (version 19, IBM Crop) was used for the statistical analysis. *P* value was considered significant if <0.05. The Chi-square test was used to analyze the discrete variables, whereas student *t*-test was used to analyze the differences in means.

Results

The study enrolled 56 patients with a median age of 39 years (range 14–85) with 4:1 female-to-male ratio as shown in Table 1. Although the (mean ± standard deviation [SD]) duration of illness before enrollment was 5 (2.2) years, almost two-thirds of them were

nonsplenectomized for a variety of reasons or contraindications.

Efficacy

the response rate 75% of the patients was recorded during the meantime 29.3 weeks of treatment. The time to initial response was 2.5 weeks and the mean dose of romiplostim used to achieve a sustained response was 3.1 mcg/kg, as shown in Table 2. Moreover, in parallel to improving platelet count, none of the responders developed any bleeding event while on treatment. On the other hand, 7/14 (50%) of nonresponders, who all had have a history of bleeding event(s), reported no more such event(s) while they were followed during the study in spite of still low platelet counts.

Because of a shortage of romiplostim for a period in the centers where the study conducted, we managed to discontinue treatment for patients who had already achieved platelet count above 100 × 10^9/L, that had sustained with small doses (1–3 mcg/kg) without need for adjustment during the preceding 4 weeks, and followed them weekly to resume treatment when required. Interestingly, 12 (28.6%) patients among the responders succeed to maintain a safe platelet count with every other week dose of romiplostim, and 2 (4.8%) patients have remained without treatment over a median follow-up period of 5 months, a disease response which could be equal to "remission" [Table 2]. The two patients who had remission were both females, splenectomized and failed to respond to a variety of therapeutic options including steroid, IVIG, immunosuppressive therapy, and rituximab.

Further sub-analysis of response rate among study groups, we noticed that the response rate was significantly higher 94.4% versus 65.8% among nonsplenectomized, *P* value was 0.018. No significant difference was found in relation to gender and the duration of illness between responders and nonresponders, as shown in Table 3.

Safety

Among the 56 patients enrolled in this study, 32 (57.1%) patients developed at least one adverse effect during the treatment. The most frequent complaint was joint pain, recorded in 35.7% of patients, followed by headache (32.1%), fatigue (21.4%), low-grade fever (16.07%), dizziness (14.2%), itching (7.1%), and nasopharyngitis (3.5%). These symptoms occurred mainly on the day of taking the dose through the next 2 days were mild-to-moderate and could be managed by simple medications. In addition to that, significant anaphylactic reaction, manifested as fever, urticaria, eryrthroderma, and facial swelling occurred in one patient shortly after the 1st two injections, which actuated us to omit further doses, and so, to exclude her from the study.

Table 1: Basic characteristics of the studied patients

Variable	Value
Number of patients	56
Median age (range) years	39 (14-85)
Gender: Female/male	45/11
Duration of disease (mean±SD)	5±2.2
Splenectomy: Yes/no	18/38

SD=Standard deviation

Table 2: Efficacy of romiplostim

Variable	Value (%)
Response rate	42 patients (75)
Bleeding events among	
Responders	0/42 (zero out of 42)
Nonresponders	7/14 (7 out of 14)
Mean time to initial response±SD (weeks)	2.5±0.8
Mean dose to sustained response±SD (mcg/kg)	3.1±1.1
Responders	
On every other week dose	12 patients (28.6)
In remission (off treatment)	2 patients (4.8)

SD=Standard deviation

Table 3: Characteristics of responders and nonresponders

Characteristic	Response rate (%)	*P*
Splenectomized		
Yes	94.4	0.018*
No	65.8	
Gender		
Male	54.5	0.147
Female	80	
Mean duration of illness±SD (years)		
Responders	4.9±1.5	0.65**
Nonresponders	5.2±2.1	

*OR: 5.3, Degree of freedom: 1, **Measured by Student's *t*-test. OR=Odds ratio, SD=Standard deviation

Transient thrombocytosis was complicated the treatment course of six patients. Those patients managed by dose adjustment without any thrombotic event. Furthermore, no blood film morphology findings suggestive of bone marrow fibrosis. Although one patient had already some degree of renal impairment, no further (or new) deterioration in renal or hepatic functions had been noticed during the course of treatment in any of the patients. The reported adverse events are shown in Table 4.

Discussion

The current study included 56 adults' patients with symptomatic refractory ITP. Majority (75%) of them achieved satisfactory sustained response with successful gradually discontinuation of other therapeutic options.

Table 4: Adverse effects of romiplostim among the studied population

Adverse event	*n* (%)
Joint and bone pain	21 (35.7)
Headache	18 (32.1)
Fatigue	12 (21.4)
Low-grade fever	9 (16.1)
Dizziness	8 (14.2)
Itching	4 (7.1)
Nasopharyngitis	2 (3.5)
Anaphylaxis	1 (1.7)
Thrombocytosis	6 (10.7)

Others studies; Cines *et al*. and Cooper *et al*. found the response rates 75.5% and 87%, respectively. However, their target platelet count was 50–200 × 10^9/L that maintained for at least 6 of the last 8 weeks and 9 of the last 12 weeks, respectively,[11,12] as compared to at least 4 consecutive weeks in the current study. Furthermore, Japanese double-blind randomized Phase III clinical trial, Shirasugi *et al*. found that most romiplostim-treated patients (95%) achieved platelet responses for a median of 11 weeks.[13]

On sub-analysis of the current results, the response rate was significantly more among splenectomized patients, 17/18 (94.4%) versus 25/38 (65.8%). This finding was consistent with Cooper *et al*., who found that the response rates were 100% among splenectomized and 72.7% among nonsplenectomized.[11] The possible explanation of this difference is that nonsplenectomized patients have expectedly more difficult disease as the spleen is the primary site for platelet-reactive T- and B-cell activation and platelet destruction.[14] On the other hand, Cines *et al*. found that the response rate was higher among nonsplenectomized, 80% versus 68%. Their interpretation was that splenectomized patients enrolled in their study had more severe disease at baseline, as shown by the longer duration of disease, a higher proportion that had used more than 3 prior ITP treatments, and a lower baseline platelet count at study entry compared with nonsplenectomized patients.[12]

Regarding the onset of effectiveness, we found that the mean (±SD) time to get an initial response was 2.5 (0.8) weeks, and the mean (±SD) dose of romiplostim used to achieve a sustained response was 3.1 (1.1) mcg/kg. In other clinical studies, most patients who responded to romiplostim achieved and maintained platelet counts ≥50 × 109/L after 2 weeks with a median dose of 2 mcg/kg.[9,10,15]

After a single romiplostim injection, the duration of action can extend to 28 days, with half-life range of 1–34 days. Despite that, it is recommended to be administered as weekly dose.[9,10] Accordingly, we found that 28.6% of responders could maintain stable platelet counts with every other week dose. However, those patients were still scheduled for weekly follow-up visits during the study period, but on long-term view with maintained safe platelets counts the patients might be came on the same day of their potions. Certainly, this will have a positive impact on patients' convenience and compliance, safety profile, cost, and health services workload. However, those patients should be selected and monitored carefully.

Furthermore, when the treatment had to be discontinued as romiplostim became no longer available due to a supply shortage, two patients among responders (4.8%) were noticed to be in remission, i.e., stable, safe platelet counts without any treatment, after a median follow-up period of 23 weeks. Carpenedo *et al*. found that 27/30 patients (90%) responded to romiplostim, and 13 patients among the responders (48%) could achieve stable, safe platelet counts, and were able to stop treatment after a mean of 43.3 weeks on therapy with sustained response maintained at a mean of 28.8 months. In 5 patients among those 13 with long-term remission, romiplostim seemed to be the only responsible treatment.[16] Newland *et al*. found that the overall response rate was greater than 90%, and remission was observed in 32% of patients for a median of 11 months. However, patients enrolled in their study were with ITP for ≤6 months, which put a potential of spontaneous remission.[15] Provan *et al*. found that 19 patients (90.4%) responded without concomitant ITP therapy, of whom, 5 patients (26.3%) achieved remission for longer than 6 months after discontinuing romiplostim. The median duration of therapy was 32 months.[17] Indeed, the low rate of remission among our patients in comparison to these studies could be attributed to the limited study time with relatively short duration of romiplostim therapy, mean (±SD): 28.3 (10.2) weeks.

In addition to that, 7 of the 14 nonresponders started to experience no more bleeding events while they were on romiplostim despite low platelet counts. This could be attributed to TPO-RA-induced improvement in collagen-dependent aggregation and platelet glycoprotein VI levels, hence, improving platelet function.[18] This raise the question whether to continue the treatment for those patients despite no response in view of platelet counts. Further studies might be needed to address the answer.

Regarding safety, romiplostim seemed to be safe and well tolerated for most of the studied patients. Symptom wise, the most frequent complaint was joint pain (35.7%), followed by headache, fatigue, low-grade fever, dizziness, itching, and nasopharyngitis. Most of these adverse effects were mild to moderate, self-limited or

required simple medications. One patient developed an anaphylactic reaction shortly after the 1st two injections, which could not be attributed to another cause, therefor, further doses were omitted, and as mentioned, the patient was excluded from the study. Our results have been close to some global research.[11-14]

Investigation wise, fluctuating platelet response for a given dose was a recognized problem in some patients, whom required careful monitoring and dose adjustment. However, six patients developed thrombocytosis on at least one occasion, ranged from 480 to 1650 ($\times 10^9$/L), fortunately, without any thrombotic event. Secondary marrow fibrosis might occur in ~3% of patients treated with long-term TPO-RA such as romiplostim, but it is usually reversible and dose dependent.[10,19] Fortunately, we did not find any blood picture suggestive of marrow fibrosis during the study follow-up period. This could be due to the limited time of the study. However, absence of teardrop poikilocytosis and leukoerythroblastosis on peripheral blood smears could not certainly exclude occurrence of some degree of reticulin deposition which might progress to a clinically evident marrow fibrosis.[10]

Conclusions and Recommedations

Romiplostim is an effective option in more than 2/3 of patients with refractory ITP as a long-term treatment or as a bridge for another intervention, with a relatively safe toxicity profile. The response rate is higher among splenectomized patients. However, in view of the observed onset of initial response, romiplostim seems to be not useful as a rescue therapy when an urgent rise in platelet count is required.

Larger scale study with longer duration is recommended to overcome the limitations of the current study and to answer the question about continuity of romiplostim among clinically responders but with low platelets' levels.

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Conflicts of interest
There are no conflicts of interest.

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