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Assessment of the immunomodulatory cytokines interleukin-35, interleukin-10, and transforming growth factor-β in patients with idiopathic immune thrombocytopenia purpura on treatment with romiplostim: A cross-sectional analysis

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Abstract:

BACKGROUND: Idiopathic immune thrombocytopenia purpura is an autoimmune bleeding disorder that accounts for approximately one-third of clinical hemorrhagic diseases. Pathophysiologically, it involves a complicated imbalance in the immune system.

OBJECTIVES: This study focuses on evaluating the levels of the immunomodulatory cytokines interleukin (IL)-35, interleukin-10, and transforming growth factor-β (TGF)-β in patients with refractory idiopathic immune thrombocytopenia undergoing treatment with romiplostim.

MATERIALS AND METHODS: A cross-sectional study encompassed 78 individuals with idiopathic immune thrombocytopenia and conducted measurements of different immunomodulatory cytokines in response to different responses of idiopathic immune thrombocytopenia patients on romiplostim therapy. The research was carried out from May 1, 2025, to September 1, 2025, and it was conducted at the Haematology and Bone Marrow Transplant Centre, Medical City, Baghdad, Iraq.

RESULTS: More than half of them have responded to romiplostim 52 (66.7%) with a mean dose of 103.8 mcg. The study demonstrated a notable link between immunomodulatory cytokines (IL-10, IL-35, and TGF-β) and platelet count; however, no significant difference was found between responders and nonresponders regarding these cytokines.

CONCLUSIONS: Romiplostim demonstrated effective management in Iraqi patients, and the Treg cells and their associated cytokines (IL-35, IL-10, and TGF-β) may contribute to immune system dysregulation in adult patients with chronic idiopathic immune thrombocytopenia.

Keywords:

Lmmune thrombocytopenic purpura, immunomodulatory cytokines, interleukin-10, interleukin-35, romiplostim, thrombocytopenia

Introduction

Idiopathic immune thrombocytopenia purpura (ITP) is an autoimmune bleeding disorder and is considered approximately one-third of clinical hemorrhagic diseases.[1,2] Pathophysiologically, it involves a complicated imbalance in the immune system.[3] Both environmental and genetic

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factors are thought to play an important role in disease development. Different genes involved in immune system regulation, including cytokines, human leukocyte antigen genes, FcYR, and cytotoxic T-lymphocyte-associated protein-4, are associated with increased ITP susceptibility in several studies.[4] CD40 plays an important role in mediating immune responses, and its polymorphisms can increase disease susceptibility.[5,6] Its impact on cellular immune responses (macrophages, T-cells, etc.) and humoral (B-cell lymphocytes) in patients with ITP treated with romiplostim is significant.[7] The abnormal expression of CD40 induces pro-inflammatory cytokines, giving rise to the development of autoimmune diseases.[8] As a result, this effect on pro-inflammatory responses altered both humoral and cellular immunity in ITP patients, which may influence the effectiveness of romiplostim by modifying the immune landscape.[9,10]

TGF-β is one of the most essential cytokines in T-cell regulation. It is produced in response to almost all immune cells, and it regulates both adaptive and innate immune responses.[11,12] Active ITP is a manifestation of Th1 and Th17 cytokine abnormality, which may result from a lack of Treg suppression of autoimmunity.[13,14] There is an inverse relationship between lowered Treg activity and Th1/Th17 cytokines, and the common factor associated with this inverse relationship is the increase in platelet counts in ITP patients after treatment with different therapies, since platelets contain high amounts of TGF-β that switch to induce Treg production.[15-21]

The high levels of autoreactive plasma cells, together with B-cell activating factor, have been strongly associated with ITP and other autoimmune diseases.[22,23] Regulatory B cells (Bregs) have an essential role in maintaining peripheral tolerance by inducing IL-10 secretion, which has an important role in limiting immune activation of adaptive and innate immune cells through enhancing Treg and reducing autoreactive Th cell functions.[24,25] Hence, any impairment in Bregs promoted peripheral tolerance in B-cell compartments.[13,22,24,25]

IL-35's main functions include proliferation of conventional T suppression and conversion of naive T conv cells to a suppressive (iTr35)-induced Treg cell.[26-28] It plays an immunomodulatory role and inhibits both cytokines and pro-inflammatory cells by inducing the secretion of both IL-10 and TGF-β and the production of Treg and Breg cells.[29] IL-35 plasma concentration was correlated with platelet count; this may make it a biomarker that reflects the activity of ITP.[30] Various prior studies examine the response to Romiplostim[31-33] and its correlation with the levels of regulatory cytokines IL-35, IL-10, and TGF-β;[34-36] however, the precise influence on critical regulatory cytokines is ambiguous, and predictive biomarkers for response are absent. Therefore, this study aims to evaluate the levels of the immunomodulatory cytokines IL-35, IL-10, and TGF-β in patients with refractory ITP undergoing treatment with romiplostim.

Patients, Materials, and Methods

Study design

A descriptive cross-sectional design was carried out from May 1, 2025, to September 1, 2025, to measure romiplostin treatment response in relation to immunomodulatory cytokines among patients with ITP in the Haematology and Bone Marrow Transplant Center, Medical City, Baghdad, Iraq.

Patients and eligibility criteria

The study involved 78 patients diagnosed with chronic ITP, who were selected according to the diagnostic criteria of the Iraqi haematologists' consensus.[37] Inclusion criteria include persistent/chronic ITP patients, age above 14 years old, and adherent patients on romiplostim, while exclusion criteria include pregnant women, age <14 years old, chronic illnesses such as DM type 1, IHD, and autoimmune disease, and a recent history of acute infection.

Ethical considerations

The study was approved by the University of Baghdad-College of Pharmacy Research Ethics Committee with approval number (RECO62447H). The study followed the Declaration of Helsinki. All patients actively participated and gave written consent beforehand.

Data collection and measures

All patients were diagnosed and categorized based on platelet count after receiving romiplostim. Seventy-eight patients who have steroid-refractory ITP and are on romiplostim treatment were recruited in the study and divided into two groups (responders and nonresponders). The definition of a complete response is a platelet count after treatment $\geq 50 \times 10^9$/L,[37] and nonresponse is $<50 \times 10^9$/L.[38]

The response criterion of treatment was to reach a safe platelet count that was sustained for at least 4 weeks. Patients who succeeded in reaching this target (platelet count after treatment $>50 \times 10^9$/L) were considered "responders," while those who did not reach a platelet count of 50×10^9/L after 4 successive weeks of the maximum dose of romiplostim were called "non-responders."[38]

- The initial starting dose of romiplostim is adjusted and weekly increased according to platelet count and bleeding[37]
- Anemia is generally defined by hemoglobin levels, with a diagnosis of anemia for women

when <12 g/dL (120 g/L) and for men when levels are <13 g/dL (130 g/L)[39]
- Bleeding tendency is a medical problem that is usually caused by a decreased count of platelets[40,41]
- Platelet count is the measure of the number of platelets in the blood[42]
- All databases were collected using a direct questionnaire data sheet. Demographic data (age and sex) and hematologic parameter changes were documented.

Measurement tools

Serum levels of IL10, IL35, and TGF-β were measured by sandwich-type enzyme-linked immunosorbent assay (ELISA) using the corresponding human ELISA kits purchased from Sunlong for both IL10 and TGF-β and BT Lab for IL35 (China). The measurements were performed using a HumaReader HS microplate reader.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics version 24 is developed and produced by IBM Corp., which is headquartered in Armonk, New York, USA. Continuous variables were presented as mean ± standard deviation. Categorical variables were represented as numbers and percentages. Nonparametric tests were utilized to show the associations between sociodemographic and clinical characteristics of the participants and illness perceptions (Mann–Whitney *U* test for two groups and Kruskal–Wallis for more than two groups). Data were considered statistically significant when $P < 0.05$.

Results

Out of 78 ITP patients recruited in this study, most of them were at an age lower than forty, and 59 (75.6%) were female, resulting in a female-to-male ratio of approximately 4:1; about 40 (51.3%) patients had anemia and 33 (42.3%) had bleeding [Table 1].

More than half of them have responded to romiplostim 52 (66.7%) with a mean dose of 103.8 mcg [Table 2].

The concentrations of IL-35 ranged from 1.5 to 21.6 pg/mL, IL10 from 39.8–110 pg/mL, and TGF-B from 170 to 735 pg/mL, with no significant differences seen between responders and nonresponders for any mediators listed [Table 3].

The results indicated no correlation between studied immunomodulatory cytokines and patient variables, except for platelet count, which exhibited a robust connection with a *P* value ranging from 0.7–0.8 [Table 4].

Table 1: Patient characteristics (*n*=78)

Variable	*n* (%)
Age	
<40	35 (44.9)
40-60	28 (35.9)
>60	15 (19.2)
Sex	
Male	19 (24.4)
Female	59 (75.6)
Anaemia	
Yes	40 (51.3)
No	38 (48.7)
Bleeding	
Yes	33 (42.3)
No	45 (57.7)

Table 2: Romiplostim treatment response of immune thrombocytopenia purpura patients (*n*=78)

Variable	Groups	
	Response	No response
Romiplostim response	52 (66.7)*	26 (33.3)*
Romiplostim dose (μg)	103.8±60**	157.7±65**
Platelet count	108.1±45.7**	26.4±4.9**

*(%), **Mean±SD. SD=Standard deviation

Table 3: Different studied immunomodulatory cytokines' levels among immune thrombocytopenia purpura patients (*n*=78)

Variable	Mean±SD	*P*
IL35 (pg/mL)		
No response	6.26±6.8	0.649
Response	5±2.8	
IL10 (pg/mL)		
No response	56.9±13.6	0.436
Response	59.6±15.6	
TGF-B (pg/mL)		
No response	303.2±192	0.652
Response	267.9±64	

P-value for a Mann–Whitney *U*-test. SD=Standard deviation, IL=Interleukin, TGF-B=Transforming growth factor-beta

Table 4: Studied immunomodulatory cytokines and different patient-related variables (*n*=78)

Variable	IL-35		IL-10		TGF-B	
	r	*P*	*r*	*P*	*r*	*P*
Age	−0.177	0.479	0.020	0.448	−0.177	0.538
Sex	0.061	0.572	0.113	0.509	0.061	0.461
Anemia	−0.19	0.535	0.088	0.416	−0.019	0.5
Bleeding	0.71	0.321	−0.024	0.467	0.070	0.351
Platelet count for all	0.845	0.47	0.794	0.483	0.848	0.465
Romiplostim response	0.052	0.427	0.089	0.737	0.051	0.469

The *P*-value indicates significant differences according to the Chi-square test, and the *r*-value indicates Spearman's rank correlation coefficient. IL=Interleukin, TGF-B=Transforming growth factor-beta

Table 5 demonstrates that none of the immunomodulatory cytokines exhibited a statistically significant AUC for identifying responders to romiplostim. IL-35 (≤4.2 pg/ml, sensitivity 61.54%, specificity

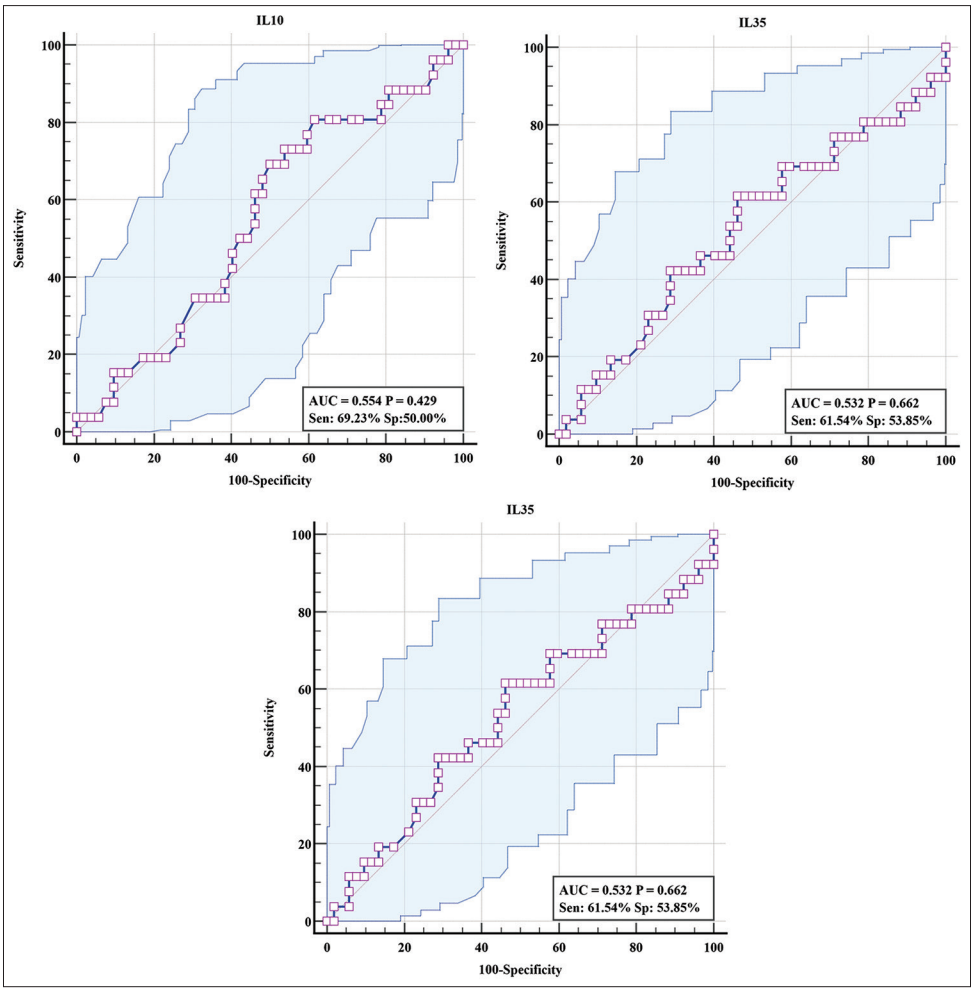

Figure 1: Receiver operating characteristic curve of the studied immunomodulatory cytokines for identifying romiplostim responders in immune thrombocytopenia purpura patients

Table 5: Receiver operating characteristic curve analysis for immunomodulatory cytokines in identifying responders (*n*=78)

Variable	AUC	Cut-off value (pg/mL)	Sensitivity (%)	Specificity (%)	*P*
IL-35	0.532	≤4.2	61.54	53.85	0.662
IL-10	0.554	≤53.3	69.23	50	0.429
TGF-B	0.531	≤242.1	61.54	53.85	0.666

IL=Interleukin, TGF-B=Transforming growth factor-beta, AUC=Area under the curve

53.85%), IL-10 (≤53.3 pg/ml, sensitivity 69.23%, specificity 50%), and TGF-β (≤242.1 pg/ml, sensitivity 61.54%, specificity 53.85%), as illustrated in Figure 1.

Discussion

This study comprised 78 individuals with ITP, with a predominance of females at a ratio of 3:1, consistent with findings from a study conducted in Jordan.[43] Romiplostim effectively manages Iraqi patients with mild to moderate side effects,[44] achieving a response rate of 52 (66.7%) with a mean dose of 103.8 mcg (±60), which surpasses the response rate of 75% reported in another study conducted in Baghdad and Basra.[31] Both studies conducted in Iraq showed a lower response rate than other studies in Iraq, the United States, and the European Union: 87% and >82%, respectively.[32,33] This may pertain to the temporary scarcity of Romiplostim at the study sites, which resulted in the cessation of treatment for patients who had attained a platelet count exceeding 100 × 10^9/L, maintained with minimal doses (1–3 mcg/kg) without necessitating adjustments over the prior 4 weeks and were monitored weekly to recommence treatment as needed.[31] Medication shortage in the public hospitals was the main barrier facing physicians in implementing treatment guidelines.[45] Physicians from different specialties in Baghdad showed a tendency to prescribe lower than recommended doses for different reasons, among which is a shortage in the supply of the drug; however, they believed that this practice may disadvantage the patient due to concerns about efficacy and safety.[46] Concerning the repercussions of ITP, around 33 (42.3%) patients continue to experience bleeding, a rate that exceeds the bleeding percentage

observed in Jordanian ITP patients, which is 18 (21.6%).[44] This bleeding may be the underlying cause of the anemia, which was observed in around 40 cases (51.3%).

The IL-35 mean of the plasma level was 5.43 ± 4.4, which is lower than that observed in other studies conducted in China, which included both ITP patients and healthy controls, measured at 165.30 ± 16.49 pg/ml and 101.30 ± 8.31 pg/ml, respectively.[47-49] Despite the expression of IL-35 receptors on megakaryocytes facilitating megakaryopoiesis and enhancing the response rate and diminishing bleeding symptoms in people with ITP,[50] The results indicated that IL-35 levels exhibited no significant variations between responders and non-responders, and demonstrated no correlation with patient characteristics, except for platelet count, which revealed a strong relationship with a r value of 0.71. This result is similar to another study conducted in Egypt; there was no statistically significant association between IL-35 levels and the patient groups, which included adults diagnosed with primary ITP and controls.[34]

The IL-10 range was 39.8–110 pg/mL, indicating a robust correlation between immunomodulatory cytokines and platelet count, with r = 0.79, which aligns with another study conducted in China that demonstrated a significant association between plasma IL-10 levels and platelet counts in ITP patients. However, while serum IL-10 levels were markedly lower in active ITP patients compared to those in remission,[35] there was no significant difference between responders' and nonresponders' patients. The preceding investigation conducted in Iraq among pediatric patients indicated that the mean blood IL-10 concentrations in ITP patients were also lower than those in control children. However, this difference did not achieve statistical significance,[51] while various research conducted in Egypt indicated contrasting results, demonstrating a substantial inverse connection between IL-10 levels and platelet counts.[52-54]

The mean concentration level of TGF-β was 280 ± 124, revealing no significant difference between responders' and nonresponders' patients, nor any correlation with patient variables, except for platelet count, which exhibited a strong correlation of r = 0.84. This finding aligns with a study conducted in Iraq, which reported a strong correlation between circulating TGF-B1 levels and platelet counts, with r = 0.8, indicating that low circulating TGF-B1 levels increase as platelet counts improve following various treatments. Similar results had been shown in other countries.[20,36,55-57] The majority of the previously referenced studies, compared with our results, did not rely solely on romiplostim but rather on other treatments used to achieve remission. This may elucidate the causes for the differential cytokine levels (IL-35, IL-10, TGF-β) seen between these investigations. The AUC for all examined cytokines (IL-35, IL-10, TGF-β) was <0.56, indicating that none of the aforementioned immunomodulatory cytokines can serve as biomarkers for the assessment of ITP treatment response.

Treg and its cytokines (IL-35, IL-10, and TGF-β) may be integral to the pathophysiology of adult chronic ITP, since they facilitate the preservation of peripheral immunological tolerance,[58] so it is important to highlight the complexity of ITP pathophysiology and the need for further research to elucidate the precise mechanisms underlying IL-10, IL-35, and TGF-β levels' impact on disease progression and treatment outcomes. More research is needed to understand the mechanism and their function, which may be viable targets for ITP immune modulation.

Study limitations

The restricted cohort of ITP patients, which may pose a considerable constraint, along with the insufficient collaboration of the participating patients.

Conclusion

Romiplostim demonstrated effective management in Iraqi patients, with the study revealing a significant correlation between immunomodulatory cytokines (IL-10, IL-35, and TGF-β) and platelet count; concurrently, no significant difference was observed between responders and nonresponders concerning these immunomodulatory cytokines.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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