

Evaluating the Role of IL-6-174 C/G (rs1800795) Gene Polymorphism in Modulating Serum Levels of Some Inflammatory Biomarker and Therapeutic Outcomes with Rituximab in Iraqi Rheumatoid Arthritis Patients

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Abstract

Rituximab is a chimeric monoclonal antibody used in the treatment of Rheumatoid Arthritis (RA). However, patients receiving it show various degrees of responsiveness without knowing the exact causes behind this diversity. Interleukin-6 (IL-6), among other inflammatory biomarkers, is involved in RA pathogenicity. This study investigated the role of IL-6-174 G/C (rs1800795) gene polymorphism at the promoter region and its possible effect on serum level of different inflammatory biomarkers and response to Rituximab (RTX) among RA patients, and whether this genotyping can aid clinicians in choosing eligible patients for RTX. Ninety adult RA patients from the Rheumatology Unit of Baghdad Teaching Hospital were recruited for this cross-sectional study. All were receiving RTX intravenously plus Methotrexate (MTX). Blood samples were taken from all the candidates for genetic analysis. Serum levels of IL-1 beta, IL-6, TNF- α (Tumor Necrosis Factor) were measured, and their effect on Rituximab response was assessed using disease activity score in 28 joints (DAS 28 score). From the pooled 90 patients 50 of them were RTX-responders, while 40 were non-responders. Regarding the studied Single Nucleotide Polymorphism (SNP). The genotype distribution was in Hardy-Weinberg equilibrium ($p=0.378$). The proportion of patients with G allele was significantly higher in the RTX-responders (73%) compared to RTX non responders (45%) ($P\text{-value}<0.001$). The level of IL-6 was significantly higher in the CC genotype (48.06 ± 23.53) compared to the GC phenotype (36.97 ± 19.57) and GG phenotype (26.48 ± 18) ($P\text{-value}=<0.001$). As conclusion for optimizing RTX treatment among RA patients, the genotyping study of the promoter region of IL-6 could be a valuable marker, different alleles at rs1800795 affected the serum levels of different inflammatory biomarkers and extended to affect RTX response showing that GG genotype may lead to bigger chance of response to RTX treatment than GC and CC genotypes.

Keywords: Genetic Polymorphism, IL-6, Response, Rheumatoid arthritis, Rituximab.

Introduction

Among autoimmune diseases, Rheumatoid arthritis (RA) is one of the most common one, characterized by chronic systemic inflammation that primarily affects synovial joints, leading to progressive cartilage and bone destruction as well as extra-articular manifestations⁽¹⁻³⁾. Despite advances in understanding its pathogenesis, the exact etiology of RA remains incompletely comprehended, reflecting the complex interplay between genetic susceptibility, immune dysregulation, and environmental triggers⁽⁴⁻⁵⁾. This complexity leads to significant differences in the presentation of the disease and response to therapy. In recent years, RA

treatment has evolved substantially through the introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs). They improved the clinical outcomes; however, failure in response remains a major challenge. A considerable proportion of patients exhibit inadequate response, partial response, or secondary loss of efficacy over time⁽⁶⁻⁷⁾. Such treatment failure is associated with increment in costs, persistent high disease activity, and diminished health-related quality of life. Consequently, finding biomarkers that can predict treatment response has become a key priority in individualized or personalized RA management plan⁽⁷⁾. Rituximab

(RTX), chimeric monoclonal antibody designed to target CD20 antigen on the surface of B lymphocytes, is one of the established therapeutic options for RA patients with inadequate response to conventional therapies⁽⁸⁾. B cells plays a crucial role in the pathogenesis through the production of autoantibody, antigen presentation, plus cytokine secretion⁽⁹⁾.

RTX exerts its therapeutic effect by depleting CD20-positive B cells, thereby interrupting downstream inflammatory pathways. Nevertheless, clinical response to RTX varies considerably among patients, suggesting that underlying biological and genetic factors may influence treatment outcomes⁽¹⁰⁾. Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine that plays a pivotal role in RA pathogenesis by promoting synovial inflammation, osteoclast activation, autoantibody production, and systemic manifestations of the disease. Importantly, IL-6 and B cells are functionally interconnected: B cells are a significant source of IL-6, while IL-6 supports B-cell survival, differentiation, and resistance to apoptosis. Consequently, elevated IL-6 activity may reduce the effectiveness of B-cell-depleting therapies such as RTX by sustaining inflammatory and immunological pathways despite B-cell depletion⁽¹¹⁾. Single nucleotide polymorphism (SNP) within IL-6 promoter region gene, particularly the -174 G/C (rs1800795), has been related to affecting IL-6 transcriptional activity and serum level of circulating cytokine⁽¹²⁾. Studies have linked this SNP to disease susceptibility, severity, and therapeutic outcomes in some autoimmune disorders, like rheumatoid arthritis. However, findings regarding its predictive value for RTX response remain limited and inconsistent across different populations⁽¹³⁾. To date, evidence addressing the association between IL-6 -174 G/C polymorphism, circulating inflammatory biomarkers, and RTX therapeutic response in Iraqi patients with rheumatoid arthritis is lacking. Clarifying this link may support treatment stratification and the development of personalized therapeutic strategies. Therefore, this study aimed to investigate whether the IL-6 -174 G/C (rs1800795) promoter gene polymorphism is associated with the serum levels of key inflammatory biomarkers and therapeutic response to RTX among Iraqi patients with RA. This work hypothesized that genetic variation in IL-6 promoter region influences

inflammatory activity and affect clinical responsiveness to RTX therapy.

Patients and Methods

Ninety adults patients diagnosed with RA were enrolled in this work. Participants included patients who exhibited disease activity at a high level based on the revised American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria, those receiving RTX as a sole biological therapy and taking Methotrexate only as conventional Disease modifying anti-Rheumatic disease (DMARD). The dose of RTX was 1000 mg administered two times on day 1 followed by day 14 intravenously in a 6 months cyclic pattern for at least one cycle. Receiving a second biological agent concurrently with RTX, having a second disease, chronic renal failure, chronic liver disease, or malignancy, and those receiving glucocorticoid simultaneously.

A cross-sectional study was carried out under the supervision of a Rheumatologist Rheumatology center of Baghdad Teaching Hospital in Baghdad-Iraq throughout 2023. Participants were divided into RTX -responders or RTX non responders according the reduction in their (DAS28) score which is The Disease Activity Score 28 in 28 joints employed for the assessment of RA disease activity, this score compromised of tenderness state, swelling in the 28 joints, also the 100 mm visual Analogue Scale (VAS) for the assessment of general health, plus Erythrocytes Sedimentation Rate (ESR) or C-Reactive Protein (CRP)⁽¹⁴⁾.

After at least one cycle of receiving RTX, the clinical response was defined as achieving at least 0.6 reduction in the DAS28 to a value less than 5.1 from the baseline. Non responders were defined as patients failed to achieve this reduction⁽¹⁵⁾.

A suitable venous blood sample was collected, which was divided into a gel tube for further serum study, and the other part was kept in an EDTA tube, which was used later for genetic study. Geneious software was used for the Identification of sequence variation. The first step was extracting DNA followed by performing polymerase chain reaction (PCR), sequencing, and assembly. The primer design and ELISA kits used in the study are illustrated in Table 1.

Table 1. Characteristics of primer used in the current study

Primer name	Sequence 5'-3'	Annealing-Temp. (°C)	Product-size (bp)
rs1800795-F	TGTAAAACGACGGCCAGTCTGAAGCA GGTGAAGAAAGT	60	815
rs1800795-R	CAGGAAACAGCTATGACCTTGTGGAG AAGGAGTTCATAG		

The steps of PCR and its components are summarized in Table 2,3, while the diagnostic kits are in Table 4. The ABI3730XL was used for

sequencing the results of PCR, applying the Sanger technique which was provided by Microgen a Korean corporation.

Table 2. Detailed steps of PCR cycles

Steps	Temperature in c	Time in minutes	Number of cycle
Initial Denaturation	95	5	1
Denaturation	95	00:30	30
Annealing	60	00:30	
Extension	72	00:45	
Final Extension	72	7	1
Hold	10	10	

Table 3. Number and reaction volume of PCR component calculation

Number of reaction	68 rxn	Annealing temperature of primers	60
Reaction volume/run	25 µl	Length of PCR product (bp)	815

Table 4. Diagnostic Kits used in the current study for DNA extraction and ELISA

Diagnostic Kits	Suppliers
ReliaPrep™ Blood gDNA Miniprep System, Agarose, Ethidium Bromide Solution (10mg/ml), GoTag Green Master Mix, Nuclease Free Water, TAE 40X, Quantifluor dsDNA System.	Promega, USA
RF, ACCP, TNF-α, IL1-B, IL6	Nanjing Pars Biochem CO., LTD

RF: Rheumatoid Factor, ACCP: Anti-Citrullinated Protein Antibody, TNF-α: Tumor Necrosis Factor, IL: Interleukin

Windows version 25 of the Statistical Package for Social Sciences was used to conduct data analysis. Hardy Weinberg formula was used to assess the reliability of the genetic analysis. Chi-square was used for categorical data, while the Kruskal Wallis test, binary logistic regression and multivariate analysis were used when needed. P value less than 0.05 was accepted as significant.

Results

The study included 90 patients (94.4% female) with a mean age of 55 ± 5 years. The genotype distribution for the IL-6 rs1800795 (C>G) polymorphism was in Hardy-Weinberg equilibrium ($p = 0.378$), indicating no significant deviation between the observed and expected proportions. As shown in Table 5.

Table 5. Distribution of genotype according to Hardy-Weinberg equilibrium in IL6 promoter gene

Genotype	Observed n(%)	Expected n(%)	P value
rs1800795 C>G			
GG	35 (38.9)	33 (36.6)	0.378
CG	39 (43.3)	43 (47.8)	
CC	16 (17.8)	14 (15.6)	

Chi-square Test, *: statistically significant

A significant association was seen between RTX response and type of genotype (P-value=0.001). GG genotype was carried by the greater proportion of RTX responders, whereas the non-responders carried CG genotype. The G- allele

was significantly higher among the responder group (73%) compared to RTX non-responders (45%) (P-value<0.001). As shown in Table 6, Table 7, and Figure.1

Table 6. Assessment of genotype of IL6 promoter gene (rs1800795) SNP and allele frequency according to rituximab response

Genotype	RTX responders n(%)	RTX non-responders n(%)	p-value
GG	27 (54.0)	8 (20.0)	0.001*
CG	19 (38.0)	20 (50.0)	
CC	4 (8.0)	12 (30.0)	
Allele			
G	73 (73.0)	36 (45.0)	<0.001*
C (wild)	27 (27.0)	44 (55.0)	

Chi-square test used, *: statistically significant.

Table 7. Distribution of IL6 promoter gene (rs1800795) SNP polymorphism using the three genetic models for prediction of RTX treatment response

Genotype	RTX responders n(%)	RTX non-responders n(%)	OR (95%CI)	p-value
GG	27(77.1)	8(22.9)	0.099 (0.025- 0.392)	0.001*
CG	19 (48.7)	20(51.3)	0.351 (0.096-1.280)	0.113
CC	4 (25)	12(75)	Reference	-
Dominant genetic model				
CG + GG	46 (62.2)	28(37.8)	0.203(0.060-0.691)	0.011*
CC	4 (25)	12(75)	-	-
Recessive genetic model				
CC+CG	23(41.8)	32(58.2)	2.167(1.345-3.491)	0.001*
GG	27(77.1)	8(22.9)	-	-

Binary logistic regression, *: statistically significant, OR :Odd ratio

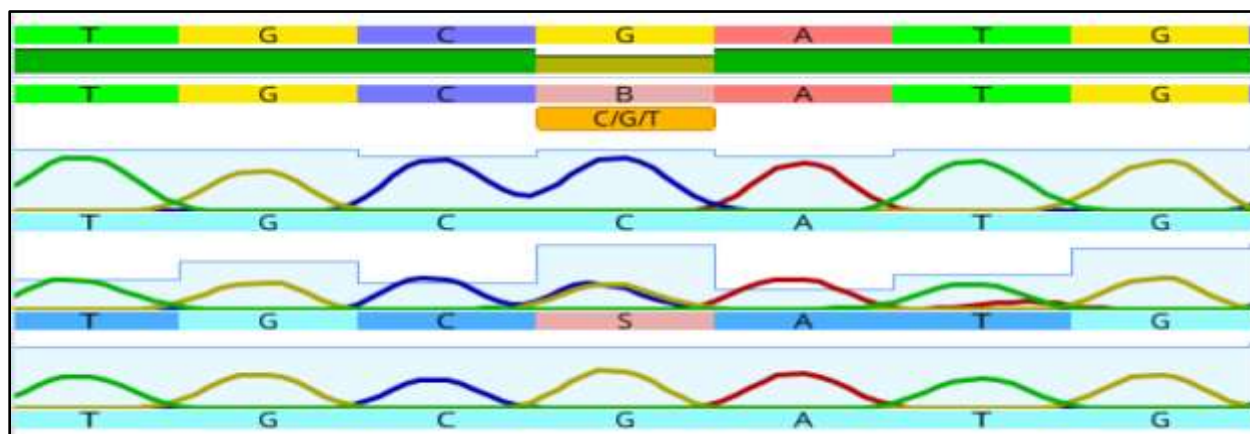


Figure 1. Analysis of SNP rs1800795 of IL6 gene using Sanger sequencing. Single “C” peak indicative of a C homozygous allele. Single “G” peak indicative of a G homozygous allele. Presence of the “C” and “G” peak indicative of C/G heterozygous allele.

In regard to rs1800795 SNP genotypes, the IL-6 was significantly higher in the CC phenotype (48.06 ± 23.53) than in both GC phenotype (36.97 ± 19.57) and GG phenotype (26.48 ± 18), with a P-value <0.001 . Likewise, the IL-1 β levels were significantly higher in the CC phenotype (7.55 ± 3.48) than in the GC phenotype (6.46 ± 2.99) and GG phenotype (4.46 ± 2.7) also with p-value <0.001 . The TNF- α levels recorded were more pronounced in the CC phenotype (118.48 ± 68.3) compared to the GC phenotype (97.8 ± 53.93) and GG phenotype (67.39 ± 56) achieving a P-value of 0.021. In addition, ACCP

and RF levels were both appreciably higher in the CC phenotype (37.23 ± 17.52 and 98.44 ± 49.43) compared to their equivalents in the GC phenotype (26.1 ± 15.81 and 80.68 ± 45.6) and GG phenotype (16.97 ± 14 and 52.14 ± 38.8), with $P < 0.001$ and 0.002 respectively. Moreover, DAS28 alterations were significantly reduced for the CC phenotype (0.06 ± 0.67) compared to values for the GC phenotype (0.63 ± 1.26) and GG phenotype (1.04 ± 1.1), with a corresponding P-value of <0.006 , as detailed in Table 8.

Table 8. Distribution of some variables according to genotype of IL6 promoter gene (rs1800795) SNP

Variables	rs1800795 SNP genotypes			P-value
	CC	GC	GG	
IL-6(ng/L)	48.06 ± 23.53	36.97 ± 19.57	26.48 ± 18	0.004*
IL-1 β (ng/L)	7.55 ± 3.48	6.46 ± 2.99	4.46 ± 2.7	<0.001*
TNF- α (ng/L)	118.48 ± 68.3	97.8 ± 53.93	67.39 ± 56	0.021*
ACCP(IU/ml)	37.23 ± 17.52	26.1 ± 15.81	16.97 ± 14	<0.001*
RF (ng/L)	98.44 ± 49.43	80.68 ± 45.6	52.14 ± 38.8	0.002*
Change in DAS28	0.06 ± 0.67	0.63 ± 1.26	1.04 ± 1.1	0.006*

Kruskal-Wallis Test, with Bonferroni post-hoc test, *: statistically significant, RF: Rheumatoid Factor, ACCP: Anti-Citrullinated Protein Antibody, TNF- α : Tumor Necrosis Factor, IL: Interleukin, DAS28: Disease Activity Score in 28 Joints.

In the final multivariate analysis model (model 4), only GGrs1800795 showed an independent relationship with treatment response with an OR less than 1 (0.021 (0.001-0.378)),

indicating that this polymorphism ensures a treatment response compared to the CC polymorphism, as illustrated by Table 9.

Table 9. Multivariate analysis of the effects of genetic polymorphism on RTX treatment response

	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)	Model 4 OR (95%CI)
GG	0.099 (0.025-0.392)*	0.101 (0.024-0.426)**	0.040 (0.005-0.321)**	0.013 (0.001-0.225)**
CG	0.351 (0.096-1.280)	0.413 (0.108-1.576)	0.276 (0.044-1.724)	0.101 (0.009-1.162)
CC	1.0	1.0	1.0	1.0

* p-value <0.05 , ** p-value <0.01 , *** p-value <0.001

Model 1: Unadjusted (Crude) OR.

Model 2: Adjusted for demographic factors (age, sex, BMI).

Model 3: Adjusted for demographics + clinical factors (disease duration, comorbidities).

Model 4: Adjusted for demographics + clinical factors + prior treatments.

Discussion

Interleukin-6 is a pro-inflammatory cytokine, which contributes crucially in the pathogenic dilemma of RA⁽¹²⁾. Genotyping analysis of the IL-6 promoter area may guide physicians in an effective therapeutic plan for the purpose of personalized therapy regarding RTX implementation in RA⁽¹³⁾.

In Iraq, this study is the first one which investigated the link between IL 6 genotyping analysis and Rituximab response among RA patients, which showed that CG genotype was commonly observed at rs1800795. In comparison Mohammed *et al.* discovered that RA patients had considerably greater levels of the GG genotype of the IL-6 SNP rs184229712 compared to the control group⁽¹⁶⁾. Furthermore, the current study results agreed in a partial way with an Egyptian study conducted by Amr *et al.* which concluded that GC genotype was the most prevalent genotype among RA diagnosed patients⁽¹⁷⁾. A Kuwaitian study by Al-Awadhi *et al.* revealed the higher frequency homozygous CC genotype of IL6 gene (rs1800795) among RA patients when compared to healthy controls⁽¹⁸⁾. Such discrepancies in genotype distribution may be related to ethnic and population-specific genetic backgrounds, variations in linkage disequilibrium patterns, and possible interactions between genetic and environmental factors influencing inflammatory pathways. In addition, differences in study design, patient characteristics, and disease phenotypes across populations may also lead to the beforementioned observed results. Collectively, these findings underscore the importance of population-specific genetic studies when evaluating cytokine gene polymorphisms in rheumatoid arthritis. For rs1800795 this SNP has been studied for its role in other disease like septic shock⁽¹⁹⁾, breast cancer⁽²⁰⁾, ocular diseases⁽²¹⁾, and end stage renal disease⁽²²⁾.

The results showed that the proportion of participants with GG genotype was significantly higher among RTX-responder in comparison with GC and CC genotypes. Additionally, most RTX-responders had G allele which was higher than the non-responders group. An Italian study that which was carried out by Fabris *et al.* found that after a period of six months of RTX therapy, absence of response to RTX was seen more frequently in the IL6 (rs1800795) CC carriers (9/21, 42.8%), unlike GC/GG carriers (29/121, 23.9%)⁽¹³⁾. A British work found that the presence of (CC) homozygosis in IL6 rs1800795 rarely led to good RTX response when compared to the other studied genotypes (CG/GG) (4.3% versus 24.4%)⁽²³⁾. This observation could be attributed on a physiological level by the relation of the modulation of IL-6 expression levels since CC

genotype at rs1800795 is related to higher IL-6 production leading to a pro-inflammatory and pro-survival milieu for B-cells. This environment may enhance the resistance ability of B cell to apoptosis and accelerate recovery after depletion, leading to shorter duration of RTX clinical response. For rs1800795, patients with the CC genotype had a significantly higher level of IL-6, IL-1 β , TNF- α , Anti-Citrullinated Protein Antibody (ACPA), Rheumatoid Factor (RF), and lower change in DAS28, this high level of inflammatory biomarker may explain the diminished response rate among carriers of the beforementioned genotype. In contrast, Fabris *et al.* revealed that insignificant differences were found in RA duration, ACPA and RF status according to the different genotypes of IL-6-rs1800795⁽¹³⁾, this may be explained by differences in sample size, patient ethnicity, or the duration of the disease at the time of recruitment. In contrast, Thayanara *et al.* concluded that there was a correlation between serum levels of IL-6 with clinical findings, such as ESR, DAS28. Also, using IL-6 as a clinical activity marker may be beneficial⁽²⁴⁾.

Limitations

This study has several limitations. Its single-center design may affect the generalizability of the findings, though the unit serves a diverse population from across Iraq. The sample size was constrained by time and funding, preventing a larger or follow-up study. Furthermore, potential confounding variables, such as varying numbers of rituximab cycles and the presence of comorbidities, could influence the results. While all participants were taking methotrexate, this was consistent across the cohort as patients on other conventional synthetic DMARDs were excluded.

Conclusion

Different allelic forms at rs1800795 of Interleukin-6 gene affected the serum levels of different inflammatory biomarkers and extended to affect RTX response, showing that the presence of GG genotype reflected a better response to RTX treatment than GC and CC genotypes. Consequently, studying the genotype of the promoter area of IL-6 gene may serve for optimizing RTX therapy among RA patients; yet, larger and more diverse population need to be assessed in the future.

Acknowledgement

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Conflict of Interest

There is no conflict of interest.

Funding

This study carried out under self-funding.

Ethics Statements

This work was performed according to the Helsinki II Declaration and gained the approval of the Ethical Committee of the College of Pharmacy at Mustansiriyah University with reference number 77 at 30/8/2023. The enrolled participants were briefed thoroughly about the anticipated targets of this study before asking for their participation consent.

Author Contribution

This work's authors contributed as follows: The conception and design is done by Aya Fawzi Talib and Mohammed Mahmood Mohammed; sample collection: Aya Fawzi Talib; analysis and interpretation of results: Mohammed Mahmood Mohammed; manuscript preparation: Aya Fawzi Talib. This final version was reviewed and approved by the authors.

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تقييم تاثير تعدد أشكال جين IL-6-174 G/C (rs1800795) على مستويات مصل الدم لبعض المؤشرات الحيوية الالتهابية والاستجابة لريتوكسيماب بين المرضى العراقيين المصابين بالتهاب المفاصل الروماتويدي

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الخلاصة

ريتوكسيماب هو جسم مضاد وحيد النسيلة خيمري يستخدم في مسار علاج التهاب المفاصل الروماتويدي ومع ذلك، فإن المرضى الذين يتلقونه يظهرون درجات مختلفة من الاستجابة دون معرفة الأسباب الدقيقة وراء هذا التنوع. يشارك IL-6 من بين المؤشرات الحيوية الالتهابية الأخرى في أمراض التهاب المفاصل الروماتويدي. بحثت هذه الدراسة في دور تعدد أشكال الجينات IL-6-174 G / C (rs1800795) في منطقة المحفز وتأثيره المحتمل على مستوى مصل المؤشرات الحيوية الالتهابية المختلفة والاستجابة لريتوكسيماب وما إذا كان المرضى التهاب المفاصل الروماتويدي، وما تأثيره إذا كان التنميط الجيني يمكن أن يساعد الأطباء في اختيار المرضى المؤهلين لهذا العلاج. تم تجنيد ٩٠ مريضاً بالغاً مصاباً بالتهاب المفاصل الروماتويدي من وحدة أمراض الروماتيزم في مستشفى بغداد التعليمي لهذه الدراسة المقطعية. كانوا جميعاً يتلقون ريتوكسيماب ويريدوا أخذ عينات الدم منهم لغرض التحليل الجيني وقياس مستويات مصل IL-1 و IL-6 و TNF وتأثيرها على الاستجابة للدواء والتي تم قياسها باستخدام درجة نشاط المرض في ٢٨ مفصلاً.

من العينة المكونة من ٩٠ مريضاً، كان ٥٠ منهم مستجيبين للريتوكسيماب و ٤٠ منهم غير مستجيبين له، وفيما يتعلق بتعدد الأشكال الجيني المدروس، لم يتم الحصول على فرق كبير بين النسبة المتوقعة والملاحظة لـ rs1800795 C>G (القيمة الاحتمالية = ٠,٣٧٨). كانت نسبة المرضى الحاملين للآليل G أعلى بشكل ملحوظ لدى المستجيبين لـ RTX (73%) مقارنةً بغير المستجيبين (٤٥%) (قيمة الاحتمالية > ٠,٠٠١). وكان مستوى IL-6 أعلى بشكل ملحوظ في النمط الظاهري CC (48.06 ± 23.53) مقارنةً بالنمط الظاهري GC (36.97 ± 19.57) والنمط الظاهري GG (26.48 ± 18) (قيمة الاحتمالية > ٠,٠٠١). كخلاصة لتحسين علاج RTX بين مرضى التهاب المفاصل الروماتويدي، يمكن أن تكون دراسة النمط الجيني لمنطقة المحفز لـ IL-6 بمثابة علامة قيمة، حيث أثرت الأليلات المختلفة في rs1800795 على مستويات المصل للعلامات الحيوية الالتهابية المختلفة وامتدت لتؤثر على استجابة RTX مما يدل على أن وجود GG يعكس استجابة أفضل لعلاج RTX من النمط الجيني GC و CC. الكلمات المفتاحية: تعدد الأشكال الجيني، المؤشرات الحيوية، الاستجابة، التهاب المفاصل الروماتويدي، ريتوكسيماب.