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The effect of Remicade Trough Level on Disease Activity in a Selected Sample of Iraqi Rheumatoid Arthritis Patients

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Abstract

Rheumatoid arthritis is a lifelong autoimmune disorder that mostly impacts the small joints, although it can affect the larger joints. Infliximab is a chimeric monoclonal IgG antibody that specifically targets tumor necrosis factor- α, an essential cause in pathogenic processes. Remicade is an original medication of infliximab. Monitoring trough levels is essential for managing disease activity. C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are utilized to detect inflammation and the drug's effectiveness. The study was designed to assess the impact of Remicade trough level on both disease activity and inflammatory biomarkers. A cross-sectional, observational study was carried out at Baghdad Teaching Hospital, involving forty-eight patients who had been diagnosed with rheumatoid arthritis (RA) based on the ACR/EULAR 2010 criteria and were on treatment with Remicade. After 3 months after starting Remicade treatment, measurements were taken for Remicade trough level, Clinical Disease Activity Index, ESR, and CRP parameters. After a 3-month course of Remicade therapy, the individuals were categorized into four distinct groups based on their CDAI scores (remission, mild, moderate, and severe groups). The Remicade trough level during the remission state was 5.6±0.12 µg/mL, in the mild disease group the trough level was 4.22±0.12 µg/mL, and in the moderate group was 2.34±0.15 µg/mL, and in severe disease activity group was 0.72±0.25 µg/ml. The CDAI in the severe group was the highest value of 20.83±3.25, in the moderate group was 14.77±0.62, mild group 5.5±0.63, and in the remission group was the least 1.34+-0.10. Furthermore, the findings indicate an inverse correlation between the Remicade trough level and the levels of ESR and CRP. The reduction in the CDAI score, ESR, and CRP were associated with a high level of Remicade in the bloodstream. This also implies that the increase in CDAI score, ESR, and CRP in patients with rheumatoid arthritis may be caused by a decrease in the level of Remicade in the bloodstream.
Keywords: Biological drugs, Infliximab, Iraqi patients, Remicade, Rheumatoid Arthritis.

Introduction

Rheumatoid arthritis (RA) is a progressive autoimmune inflammatory disease that mostly affects the smaller joints and secondary effect on the larger joints of the body [(1)]. RA is characterized by chronic pain, stiffness, tenderness, increased warmth, and inflammation in the joints [(2)]. Rheumatoid arthritis has the potential to limit movement and impede the ability to carry out everyday chores [(3)]. The prevalence of rheumatoid arthritis in the world is 1% [(4)], and in Iraq is also 1% [(5-9)]. The exact cause of rheumatoid arthritis is still unknown, although it is believed to be the consequence of a complicated interaction of genetic, environmental, and hormonal factors[(10)]. Over the years, several treatment methods have been used to improve the health of patients, reduce the number of negative occurrences, and evaluate the safety and efficacy of new active substances [(11)]. The therapy of rheumatoid arthritis (RA) may be divided into two major categories: conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and Biological DMARDs, encompassing biological originator and biosimilar DMARDs. Janus kinase inhibitors are the sole officially authorized targeted synthetic DMARDs (disease-modifying antirheumatic medicines) [(12,13)]. In another way, there are some drugs used with therapy when starting or during disease flare-ups, or during interchangeable between conventional synthetic disease-modifying antirheumatic medicines (csDMARDs) such as steroid and nonsteroidal anti-inflammatory drugs [(14,15)]. Biological anti-tumor necrosis factor medications are extremely effective therapies for Rheumatoid Arthritis [(16-18)]. Infliximab is a monoclonal antibody that blocks the action of TNF-alpha and is used for treating rheumatoid arthritis and other autoimmune disorders [(19,20)]. Biological therapy for rheumatoid arthritis (RA) is a significant success in the field of

medicine today, this is especially useful for those with rheumatoid arthritis [21,22]. effective for the treatment of psoriasis [25]. In addition, Remicade is used to treat arthritis of the spine [26]. As a result of the increasing utilization of Remicade in treating many diseases and the patent protection has expired, many companies have tried to develop similar products called biosimilars [27]. Biosimilar is a biological drug that is Remicade is a chimeric anti-TNF antibody that has recently been approved for human use by the FDA and is now available on the market [23]. In Iraqi Hospitals Remicade is used to treat several autoimmune conditions with high efficacy and safety including, Inflammatory bowel disease (IBD) [24]. Also, Remicade is highly highly similar to an approved reference drug Remicade in terms of physical, chemical, and biological properties and also safety, purity, or effectiveness [28]. According to the cost-effectiveness between Remicade and its biosimilar, the development of biosimilar has led to economic competition and a major drop in the net costs of biological therapy when many countries, approved the use of biosimilars in treating all diseases that were treated by reference product Remicade including RA [29].

Materials and Methods

Aim of study

The primary aim of this study is to evaluate the effect of Remicade trough level on disease activity.

The secondary aim of this study is to clarify the correlation between the change in trough level and inflammatory biomarkers (ESR, CRP) which are considered predictors for disease activity and treatment response.

Study design

A cross-sectional observational study was done under the supervision of a professional physician at the Center of Rheumatology/ Baghdad Teaching Hospital in Baghdad, Iraq. The study has taken place from January 2023 to January 2024.

Sample collection

The present study included a sample size 48 adult patients who were diagnosed with RA according to the criteria established by the "European League and Rheumatism Classification" and the "Revised 2010 American College of Rheumatology" [30]. In addition, all participants in this study were taking the medication Remicade regularly according to their schedule of treatment.

Inclusion criteria: Patients must have a confirmed diagnosis of RA have had Remicade medication for at least 3 months and have not taken any type of biological drug before Remicade. Furthermore, all participants should understand the study's aim and value before being enrolled.

Exclusion criteria: The study excluded patients with renal impairment, people receiving a different kind of biologic therapy, those with an ongoing infection, pregnant women, and individuals with other autoimmune disorders.

Data collection

The data was collected with a questionnaire that encompassed demographic factors such as age, gender, smoking status, family history of RA, and body mass index (BMI). Furthermore, other assessments were recorded such as the Remicade serum trough level, ESR, and CRP.

The Clinical Disease Activity Index (CDAI) was utilized to evaluate the disease's activity. The CDAI was calculated using the following formula: CDAI = TJC + SJC + PDGA + EDGA. The TJC is the tender joint count of 28 joints (0-28). The SJC is the swollen joint count of 28 joints (0-28) The PDGA is the patient disease global assessment of disease activity on a visual analog scale (VAS) (0–10). The EDGA is the evaluator/physician disease global assessment of disease activity on a visual analog scale (0–10) [31]. Remission per CDAI is defined as a score < 2.8; low or mild disease activity is when the CDAI score equals 2.8–10; moderate disease activity is with a score of 10–22; high or severe disease activity is when the score> 22 [32].

Measurement of the trough level of Remicade

To measure the trough level of Remicade the blood sample was taken just before the next dose. The blood sample was collected in a gel tube and allowed to clot. Subsequently, the clot was extracted using the process of centrifugation, conducted at a rotational speed ranging from 2,000 to 3,000 rotations per minute (rpm) for 20 minutes. The resultant supernatant was kept in deep freeze (-80 °C) till the time of analysis.

The serum concentration of Remicade is measured using solid phase enzyme-linked immunosorbent assay (ELISA) by measuring the concentration in the serum sample using (MATRIKS BIOTEK, Turkey) ELISA kit and the ELISA reader used was HumaReader HS®(Human Diagnostics Worldwide, Wiesbaden, Germany, Ref no: 16670).

The principle of the test was solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Standards and samples (serum) were incubated in the microtiter plate coated with the reactant for Remicade. After incubation, the wells were washed. Then, a horse radish peroxidase (HRP) conjugated probe was added and bound to Remicade captured by the reactant on the surface of the wells. Following incubation wells were washed and the bound enzymatic activity was detected by the addition of tetramethylbenzidine (TMB) chromogen substrate. Finally, the reaction was terminated with an acidic stop solution. The color developed was proportional to the amount of Remicade in the sample or standard. The results of samples can be determined directly using the standard curve.

Statistical analysis

The study data was entered by GraphPad Prism version 8 (RRID: SCR_002798). The P-value of ≤0.05 is statistically significant. The characteristic data was presented as frequencies and percentages; the continuous data was displayed as mean ± standard error of the mean (SEM). The investigation comprised doing correlation analysis to investigate the relationships between the data, followed by performing linear regression. The sample size calculating method was the G power sample size calculation method.

Results and Discussion

The research study consisted of a study group of 48 individuals who were diagnosed with RA and received treatment with Remicade. Table 1 provides a summary of the patient and disease features.

Table 1. Patient and disease characteristics

Variable N=48	**Results**	**%**
Age (years) Mean+-SD	57±2.16	
BMI (k2/m2)	29 ±0.21	
Duration of diseases	15±1.01	
Gender No. (%)	Male	10 (21%)
	Female	38 (79%)
Smoker status No. (%)	Smoker	9 (19%)
	Nonsmoker	39 (81%)
Marital status No. (%)	Single	11 (23%)
	Married	37 (77%)
Family history No. (%)	Yes	29 (60%)
	No	19 (40%)
Extra-articular manifestation No. (%)	Yes	20 (42%)
	No	29 (58%)

*****Data expressed as No.: number, %: percentage, Mean+ stander error of the mean.

The patients in this study were divided into four groups according to disease activity scores:
Group 1: Remission, Group 2: Mild disease
Group 3: Moderate disease,Group 4: Severe disease activity.

The patient in remission was 20 of 48 (41.66%). There were 11 mild disease activity patients (22.91%). The moderate disease group has 12 patients (25%). Only, 5 patients (10.40%) had severe disease activity as shown in Figure 1.

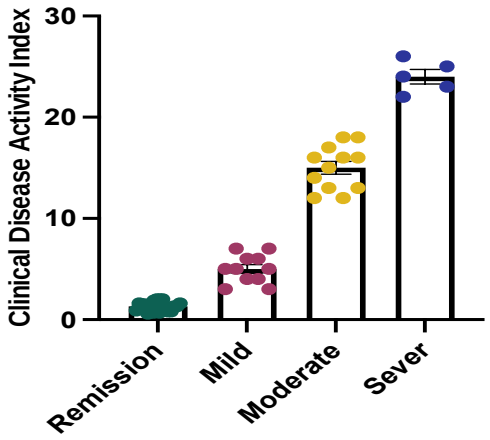

Figure 1. Distribution of patients based on clinical disease activity index.

The goal of this classification was to compare the concentration of Remicade in different groups, analyze the statistical findings, test its effectiveness in disease activity groups, and evaluate the treatment response. Remicade drug showed good efficacy with the patients of RA which explains that 41.66% of all participant patients who had RA were in remission state and the rest suffered from active diseases.

Old age, female gender, smoking history, obesity, high disease activity at the time of diagnosis, poor functional status, and elevated ESR were associated with lower remission rates. This result agrees with the findings of Merete Lund Hetland *et al* who showed that older patients are more likely to have long disease duration which may negatively affect the therapeutic efficacy of treatment [33]. Moreover, Ahmad Y. Abuhelwa *et al* proved in their study that obesity was negatively associated with RA disease remission [34]. In other words, Yasmin Khader *et al.* demonstrate in their study that men and women respond differently to the same treatment due to physiologic differences between them [35]. Moreover, Chen Yu *et al* show in their study that the smoking RA patients were predictive of poor response to Remicade treatment and heavy smokers had the poorest drug survival [36].

The results of the trough levels of Remicade between the disease activity groups are shown in (Table 2, Figure. 2), and the results were significant between groups.

This study aimed to understand the relationship between Remicade TL and disease severity in patients with RA. The variation that shows in Remicade trough levels groups is due to several reasons such as the immunogenicity or

formation of anti-drug antibodies. The immunogenicity against the biological agents is one of the most important factors that can impact on trough level of Remicade because it can induce drug clearance from the circulation and decrease its level leading to a decrease in clinical response and an increase in disease severity, these findings agreed with studies [37,38]. Nizar A. Jassim shows in his study that gender has a significant correlation with response to treatment with females being more respondents to treatment than males [39]. In addition, the differences found may also reflect genetic variation between patients as mentioned in the previous studies [40,41].

Table 2. Remicade trough level (TL) (µg/ml) according to disease activity (Remission, Mild, Moderate Sever disease status)

Colum 1	Colum 2	Colum 1 Mean + - SEM	Colum 2 Mean + - SEM	P Value
Remission (n=20)	Mild (n=11)	5.6 ± 0.12	4.22± 0.12	0.0001
Remission (n=20)	Moderate (n=12)	5.6 ± 0.12	2.34± 0.15	0.0001
Remission (n=20)	Sever (n=5)	5.6 ± 0.12	0.72± 0.25	0.0001
Mild (n=11)	Moderate (n=12)	4.22± 0.12	2.34± 0.15	0.0001
Mild (n=11)	Sever (n=5)	4.22± 0.12	0.72± 0.25	0.0001
Moderate (n=12)	Sever (n=5)	2.34± 0.15	0.72± 0.25	0.0001

*One-way ANOVA followed by Tukey's multiple comparisons post hoc test. Data expressed as mean ± SEM (Standard Error of Mean). *=P<0.05; significant results.

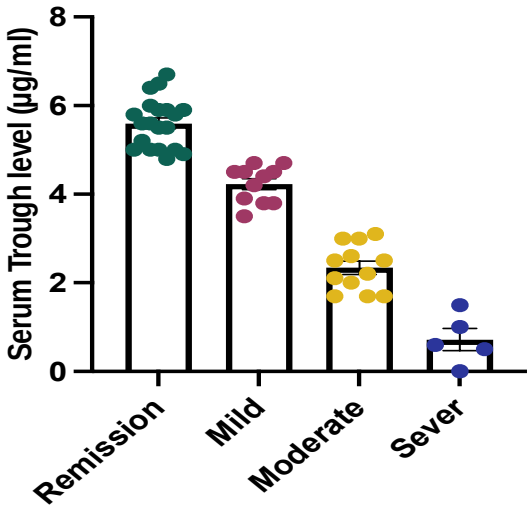

Figure 2. Serum trough level (TL) of Remicade (µg/ml) in patients, based on CDAI

The erythrocyte sedimentation rate (ESR) is an inflammatory biomarker that is used to assess the disease activity and efficacy of therapy. The ESR values in RA patients treated with Remicade were as follows: remission 15± 0.82, 25.73± 2.29, mild group, 48± 2.14 moderate group, and 68.2± 6.58for severe group.

This study evaluates the ability of the ESR to estimate disease activity and treatment responses in individuals diagnosed with RA. ESR means exhibits a significant difference between groups. The differences can show its ability in the assessment of disease severity and treatment response as mentioned by several previous studies [42-45].

C-reactive protein (CRP) is an inflammatory biomarker that is used to predict disease activity and evaluate the effectiveness of treatment. The mean ± SEM for CRP in remission was 5.05 ± 0.80 mg/l, mild group 13.09±0.85 mg/l, moderate group 24.25±1.83 mg/l, and severe group 33±2.66mg/l.

This study aims to assess the relationship between CRP levels and disease activity, as well as its potential as a predictor for treatment efficacy. The mean concentration of CRP between disease activity groups shows a significant difference among them, the finding of this study is supported by previous studies [46-49].

According to the correlation between Remicade TL, ESR, and CRP, the analysis shows a significant linear regression relationship between TL and biomarkers ($P < 0.05$). The regression lines have negative slopes, indicating that biomarker levels decline as TL increases. These biomarkers' regressions have strong R-squared values, indicating that they explain significant differences in the biomarker level as shown in Table 3 and Figure 3.

Table 3. Correlation of Remicade trough levels with ESR and CRP.

Remicade TL	Slop	R square	P value
ESR	-9.73	0.78	0.0001*
CRP	-5.60	0.84	0.0001*

*Correlation test followed by Simple linear Regression test, regression equation for CRP: Y=0.3577*X+14.29, for ESR: Y=0.7480*X+29.19, confidence intervals for the slope of CRP: 0.2288 to 0.4866, confidence intervals for the slope of ESR: 0.5311 to 0.9648, ESR: Erythrocytes Sedimentation Rate, CRP: C-Reactive Protein, *=p <0.05; significant differences.

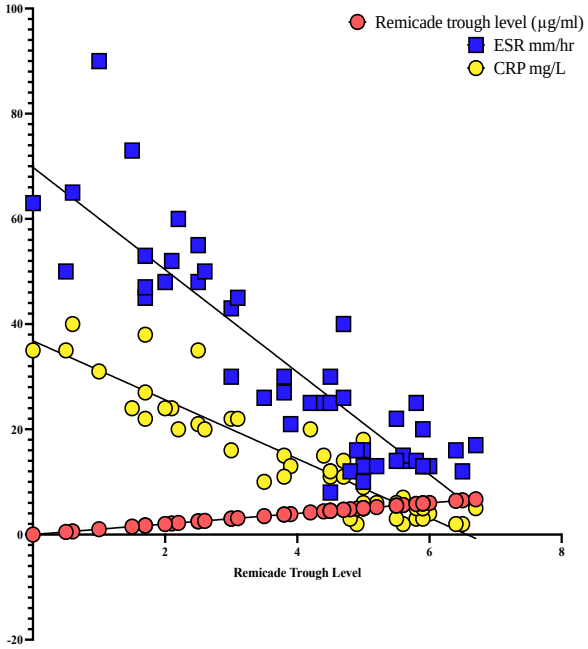

Figure 3. Correlation of Remicade trough level with ESR, and CRP

Correlations between Remicade TL and biomarkers indicate that as TL increases, the levels of the biomarkers decrease as shown in Table 3 and Figure 3.

The results demonstrate that when the drug level reaches to therapeutic level this will lead to control of disease activity and inflammation process by decreasing ESR, and CRP. This analysis agrees with the previous study [50-52], which strongly suggests that both ESR and CRP are essential biomarkers that can evaluate the disease activity and can evaluate the efficacy of treatment for patients with RA. Moreover, Mir Amir Aghdashi *et al* showed in their study that the serum level of ESR, and CRP can be a useful and reliable biomarker in determining RA activity and its severity and can also predict treatment response [53].

Conclusion

There is a clear relationship between higher levels of Remicade and a reduction in the severity of diseases, as well as a drop in inflammatory markers such as ESR and CRP. These findings suggest that the deterioration in disease severity and inflammation in individuals with rheumatoid arthritis may be caused by a reduction in Remicade trough levels.

Acknowledgment

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

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None.

Ethics Statements

The Ethics Committee of Baghdad University-College of Medicine gave its approval for this study, which was carried out following the Helsinki Declaration. (Official letter No. 2 dated 28-1-2023).

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Mohammed Qasim Yahya Malallah A. Al-Atrakji, Reem G Hussein; data collection: Reem G Hussein; analysis and interpretation of results: Mohammed Qasim Yahya Malallah A. Al-Atrakji, Reem G Hussein; draft manuscript preparation: Reem G Hussein. All authors reviewed the results and approved the final version of the manuscript.

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تأثير مستوى الريميكيد على شدة المرض في عينة من مرضى عراقيين مصابين بالتهاب المفاصل الرثوي

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الخلاصة

التهاب المفاصل الرثوي هو مرض مناعي مزمن يؤثر على المفاصل الصغيرة والكبيرة. الانفلكسماب هو نوع من انواع الاجسام المضادة IgG وحيدة النسلية والتي تعمل على تثبيط عامل نخر الورم لكونه العامل الرئيسي المسبب لمرض الرثوي. الريميكيد هو الدواء المرجعي الاول للانفلكسيماب. ان معرفة مستوى الريميكيد في مصل الدم مهم للتحكم في شدة المرض وكذلك يستخدم بروتين سي التفاعلي ومعدل ترسيب كرات الدم الحمراء للإشارة إلى وجود الالتهاب والتنبؤ بالاستجابة الدوائية.ان الهدف من الدراسة هو تقييم تاثير مستوى الريميكيد بالدم على شدة المرض والمؤشرات الحيوية للالتهاب. لقد أجريت دراسة رصدية مقطعية في مستشفى بغداد التعليمي لثمانية وأربعين مريضاً الذين شخصو إصابتهم بالتهاب المفاصل الرثوي وفقاً لمعايير ACR/EULAR 2010 ويتعالجون بالريميكيد و تم تسجيل مستوى الريميكيد بالدم وكذلك بروتين سي التفاعلي ومعدل ترسيب كرات الدم الحمراء بعد ٣ أشهر من بداية العلاج. تم تقسيم المرضى إلى أربع مجموعات وفقًا لـ شدة المرض وهي (الهدأة، شدة المرض الخفيفة، والمتوسطة، والشديدة). مستوى الريميكيد في مرحلة الهدأة (٥,٦±٠,١٢ميكروجرام/ مل) وفي مجموعة شدة المرض الخفيفة٤,٢٢±٠,١٢ ميكروجرام/مل والمتوسطة٢,٣٤±٠,١٥ ميكروجرام/مل والشديدة ٠,٧٢ ±٠,٢٥ ميكروجرام/مل. ان مقياس شدة المرض كان باعلى قيمة في المجموعة الشديدة وهي ٢٠,٨٣±٣,٢ وفي متوسطة ١٤,٧٧ ± ٠,٦٢ وفي مجموعة شدة المرض الخفيفة ٥,٥±٠,٦٣ وفي حالة الهدأة كان الاقل وهو ١,٣٤±٠,١٠. كما أظهرت النتائج وجود علاقة عكسية بين مستوى الريميكيد مع مؤشرات الالتهاب. ان الانخفاض في شدة المرض وبروتين سي التفاعلي ومعدل ترسيب كرات الدم الحمراء مرتبط بارتفاع مستوى الريميكيد في الدم وهذا يدل ايضا على أن الزيادة في درجة شدة المرض بروتين سي التفاعلي ومعدل ترسيب كرات الدم الحمراء لدى مرضى التهاب المفاصل الرثوي مرتبط بانخفاض مستوى الريميكيد بالدم.

الكلمات المفتاحية: الأدوية البيولوجية ، المرضى العراقيين، التهاب المفاصل الرثوي، إنفليكسيماب، ريميكيد.