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Research Article

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Impact of Infliximab Biosimilar (Ixifi®) Trough Levels on Disease Activity and Inflammatory Markers in Iraqi Rheumatoid Arthritis Patients

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Abstract

Background: Rheumatoid arthritis is an autoimmune inflammatory condition that impacts the small and larger joints. Ixifi® is a biosimilar medication derived from infliximab that exclusively targets Tumor Necrosis Factor-α. Serum Ixifi® trough concentration is necessary to manage disease activity in rheumatoid arthritis. ***Objective***: Assess the impact of the Ixifi® trough level on disease activity and inflammatory biomarkers. ***Methods***: A cross-sectional observational study was undertaken at Baghdad Teaching Hospital, involving forty-two patients diagnosed with rheumatoid arthritis according to ACR/EULAR 2010 criteria. After 3 months after initiating therapy with Ixifi®, the serum concentrations of Ixifi®, as well as CDAI, ESR, and CRP biomarkers, were measured. ***Results***: After 3 months of therapy with Ixifi®, the patients in the remission group had a higher concentration of Ixifi® compared to the mild, moderate, and severe disease activity groups. Ixifi® trough level in remission was 5.45 µg/ml, while in mild, moderate, and severe groups, it was 3.575 µg/ml, 2.2 µg/ml, and 0.66 µg/ml, respectively. The CDAI scores were in the severe group (26.0), moderate group (19.0), mild group (7.0), and remission group (2.0). Furthermore, the findings indicate an inverse correlation between the Ixifi® trough level and both ESR and CRP. ***Conclusions***: A drop in Ixifi® levels leads to an increase in disease severity and inflammation, while high concentrations of Ixifi® decrease disease activity, ESR, and CRP.

Keywords: Biosimilar, Iraqi patients, Ixifi®, Rheumatoid arthritis.

تأثير مستويات قاع إنفليكسيماب الحيوي Ixifi®على نشاط المرض وعلامات الالتهاب في مرضى التهاب المفاصل الرثوي العراقيين

الخلاصة

الخلفية: التهاب المفاصل الرثوي هو حالة التهابية في المناعة الذاتية تؤثر على المفاصل الصغيرة والكبيرة. Ixifi®هو دواء حيوي مشتق من إنفليكسيماب يستهدف حصريا عامل نخر الورم الفا. تركيز الداء في المصل ضروري لإدارة نشاط المرض في التهاب المفاصل الرثوي. **الهدف**: تقييم تأثير مستوى قاع Ixifi®على نشاط المرض والمؤشرات الحيوية الالتهابية. **الطريقة**: أجريت دراسة رصدية مقطعية مستعرضة في مستشفى بغداد التعليمي شملت اثنين وأربعين مريضا تم تشخيص إصابتهم بالتهاب المفاصل الرثوي وفقا لمعايير ACR/EULAR 2010. بعد 3 أشهر من بدء العلاج باستخدام Ixifi، تم قياس تراكيز المصل من Ixifi ، وكذلك المؤشرات الحيوية CDAI و ESR و CRP. **النتائج**: بعد 3 أشهر من العلاج، كان لدى المرضى في مجموعة مغفرة تركيز أعلى من Ixifi®مقارنة بمجموعات نشاط المرض الخفيفة والمتوسطة والشديدة. كان مستوى قاع Ixifi في المجموعة المغفرة 5.45 ميكروغرام/مل، بينما في المجموعات الخفيفة والمتوسطة والشديدة كان 3.575، 2.2، و 0.66 ميكروغرام/مل، على التوالي. كانت درجات CDAI في المجموعة الشديدة (26.0) ، والمجموعة المعتدلة (19) ، والمجموعة الخفيفة (7.0) ، ومجموعة المغفرة (2.0). علاوة على ذلك، تشير النتائج إلى وجود علاقة عكسية بين مستوى قاع Ixifi®وكل من ESR و CRP. **الاستنتاجات**: يؤدي انخفاض مستويات Ixifi®إلى زيادة شدة المرض والالتهاب، في حين أن التراكيز العالية من Ixifi®تقلل من نشاط المرض، ESR ، و CRP.

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INTRODUCTION

Rheumatoid arthritis (RA) is a persistent autoimmune inflammatory condition that mostly impacts the smaller joints of the body and also impacts the larger joints to a lesser extent [1]. Rheumatoid arthritis is distinguished by persistent pain, rigidity, sensitivity, elevated temperature, and inflammation in the joints. Rheumatoid arthritis can impair mobility and hinder the performance of regular tasks [2]. The prevalence rate of RA is as high as 1% [3]. The prevalence of RA in Iraq is reported to be 1% [4]. The precise etiology of RA

remains elusive; however, it is hypothesized to result from a complex interplay of genetic, environmental, and hormonal influences [5]. Various therapeutic approaches have been employed throughout the years to enhance the well-being of patients, minimize the occurrence of adverse events, and assess the safety and effectiveness of novel active compounds [6]. Rheumatoid arthritis treatment may be categorized into two main groups: conventional synthetic disease-modifying antirheumatic medicines (csDMARDs) and biological DMARDs, which include both biological original and biosimilar DMARDs. At the moment, Janus kinase inhibitors are the only targeted synthetic DMARDs that are legal [7]. Nevertheless, several medications are employed as initial therapy in RA, during disease flare-ups, or while transitioning between conventional synthetic csDMARDs [8]. Biological anti-tumor necrosis factor medicines are highly potent treatments for rheumatoid arthritis [9]. Ixifi® is a chimeric monoclonal antibody that targets tumor necrosis factor. The FDA has authorized it as a biosimilar for all qualifying uses of the reference drug Remicade® (infliximab), which treats many autoimmune diseases [10]. Biosimilars are biological products that closely resemble and do not have any significant clinical differences from an already-authorized reference product by the FDA [11].

METHODS

Study design and setting

A cross-sectional observational study was conducted under a specialized physician at the Specialized Center of Rheumatology, Baghdad Teaching Hospital in Baghdad, Iraq, during the period from January 2023 to January 2024.

Sample selection

Based on the criteria established by the European League and Rheumatism classification and the Revised 2010 American College of Rheumatology, the current investigation included a convenient sample of 42 adult patients with RA diagnoses [12].

Inclusion criteria

Patients must possess a verified diagnosis of rheumatoid arthritis and have undergone treatment with the Infliximab biosimilar (Ixifi®) for a minimum duration of 3 months. Furthermore, participants must agree to undergo the necessary tests before joining the research.

Exclusion criteria

The study excluded patients with impaired kidney function, persons receiving a different type of biological medication, those with a current infection, pregnant adults, and individuals with other autoimmune diseases.

Outcome measurements

The data was collected by a meticulously crafted questionnaire that covered demographic variables like age, gender, and smoking status, as well as physical examination, family history of RA, and body mass index (BMI). In addition, the data included the results of other examinations, such as the Ixifi® serum trough level (TL), ESR, and CRP. We used the CDAI to assess the activity of the disease. The CDAI assesses 28 joints for edema and 28 joints for pain. It also includes the patient's overall rating using a 10 cm visual analogue scale,e can classify the level of disease activity into four categories: high (more than 22), moderate (greater than 10 but not more than 22), low (greater than 2.8 but not more than 10), and remission (not more than 2.8) [13]. as well as the physician's overall assessment using a 10 cm visual analogue scale. The level of disease activity can be classified into four categories: high (more than 22), moderate (greater than 10 but not more than 22), low (greater than 2.8 but not more than 10), and remission (not more than 2.8) [13].

Ethical consideration

This study received ethical approval from the Ethical Committee of Baghdad University's College of Medicine. The study followed the principles specified in the Helsinki Declaration. We briefed all participants on the objective and recorded their agreement to participate. The number of ethical approvals is 2 on January 28, 2023, there were two ethical approvals.

Statistical analysis

GraphPad Prism version 8 (RRID:SCR_002798) was used for the entry and analysis of the data. we considered the *p*-value of <0.05 to be statistically significant. The categorical data was presented as frequencies and percentages, and the continuous data was displayed as mean±standard error of the mean (SEM). To investigate the relationships between the data, correlation analysis was performed, followed by linear regression.

RESULTS

As shown in Table 1, the research study consisted of a study group of 42 individuals who were diagnosed with RA and received treatment with Ixifi®.

Table 1: Patient and disease characteristics

Variable (n=42)		Results
Age (year)		52±18
Sex	Male	7(17)
	Female	35(83)
Smoker status	Yes	5(11)
	No	37(88)
Marital status	Single	6(15)
	Married	36(85)
BMI (kg/m^2)		27±3.2
Disease duration (year)		13±5
Family history	Yes	23(55)
	No	19(45)
Extra-articular manifestations	Yes	15(36)
	No	27(64)

Data were expressed as numbers, percentages, and mean± stander deviation.

Table 1 provides a summary of the patient and disease features. The patients in this study were divided into four groups according to disease activity scores: remission, mild disease, moderate disease, and severe disease activity. The results showed that the patient in remission is 16 out of 42, which equals 38.09%. There were 8 patients (19%) in the group with mild disease activity. There were 11 patients (26.19%) with moderate disease. Looking at the severe disease condition, 7 patients were in severe disease activity (16.6%), as shown in Figure 1.

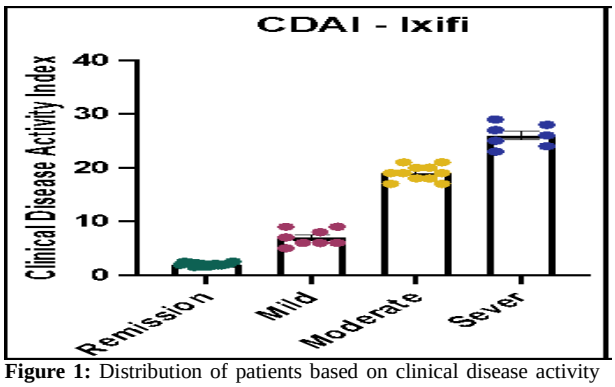

Figure 1: Distribution of patients based on clinical disease activity index.

The purpose of this categorization was to evaluate the Trough level for Ixifi® in each disease category, show the statistical result, and determine its efficacy in predicting disease activity and treatment outcomes. Initially, the average ± standard error of the mean (SEM) for the trough level of Ixifi® in remission is 5.45±0.2845 µg/ml. In the mild, moderate, and severe groups, the trough levels of Ixifi® are (3.575±0.1436 µg/ml, 2.2±0.1748 µg/ml, and 0.66±0.1435 µg/ml, respectively). When comparing the group of patients in remission with the groups of patients with mild, moderate, and severe disease, all of the statistical findings were found to be significant. The *p* values for these results were 0.0001, 0.0001, and 0.0001, respectively. These results indicate that there is a significant difference between the remission group and the other disease groups ($p<0.05$). In comparison to the moderate and severe illness groups, the mild disease group had *p* values of 0.0051 and 0.0001, respectively, showing substantial distinctions between them. Finally, the comparison between the moderate and severe groups showed a significant difference with a *p* value of 0.0071, as shown in Table 2 and Figure 2.

Table 2: Ixifi® trough levels (TL) (µg/ml) according to disease activity (Remission, Mild, Moderate Sever disease status)

Ixifi® trough levels (µg/ml)				
Colum 1	Colum2	Colum 1	Colum 2	*p*-value
Remission (n=16)	Mild (n=8)	5.45±0.285	3.575±0.144	0.0001
Remission (n=16)	Moderate (n=11)	5.45±0.285	2.2±0.175	0.0001
Remission (n=16)	Severe (n=7)	5.45±0.285	0.66±0.144	0.0001
Mild (n=8)	Moderate (n=11)	3.575±0.144	2.2±0.175	0.0051
Mild (n=8)	Severe (n=7)	3.575±0.144	0.66±0.144	0.0001
Moderate (n=11)	Severe (n=7)	2.2±0.175	0.66±0.144	0.0071

One-way ANOVA followed by Tukey's multiple comparisons *post hoc* test. Data were expressed as mean±SEM.

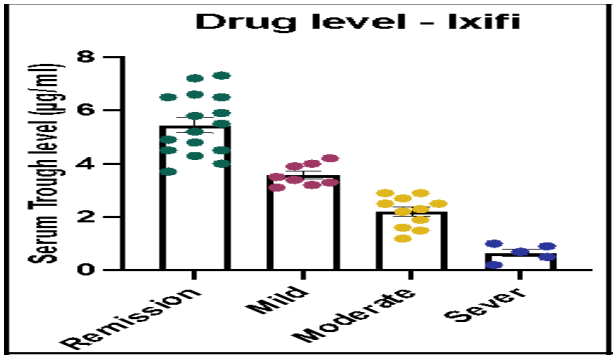

Figure 2: Serum trough level (TL) of Ixifi (µg/ml) in patients, based on CDAI.

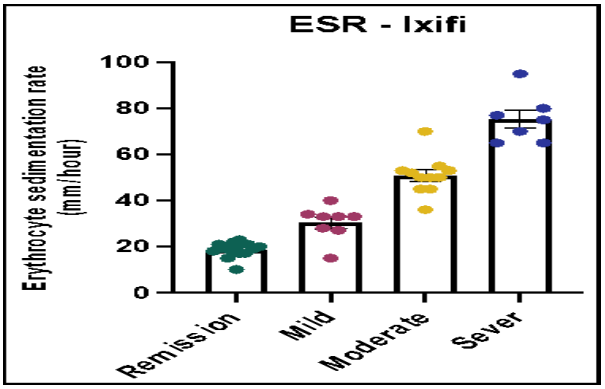

Figure 3: Erythrocyte Sedimentation Rate (ESR) expressed in mm/hr in RA-treated patients with Ixifi according to disease activity.

ESR is an inflammatory biomarker that can be used to predict the level of disease activity and assess the effectiveness of treatment. The ESR values in RA patients treated with Ixifi® were as follows: 18.65±0.7879 for the remission group, 30.38±2.605 for the mild disease group, 50.82±2.497 for the moderate disease group, and 75.29±3.944 for the severe disease group, as shown in Figure 3.

CRP is an inflammatory biomarker utilized for predicting disease activity and assessing therapy efficacy. The average ± standard error of the mean for the groups categorized as remission, mild disease, moderate illness, and severe disease were 9±1.796, 18.13±1.986, 25.82±1.457, and 35±2.828 mg/l, respectively, as shown in Figure 4.

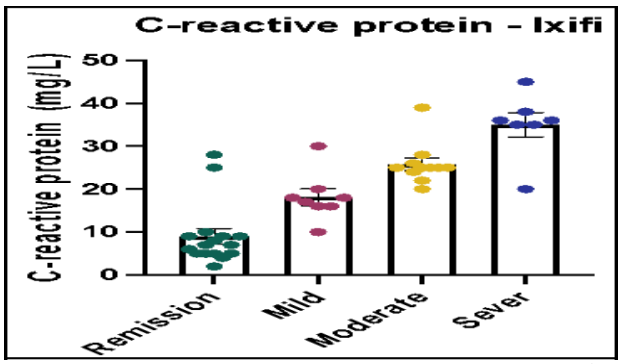

Figure 4: C-Reactive Protein (CRP) RA patient treated with Ixifi expressed in mg/l, based on disease activity.

The correlation of Ixifi® trough levels with ESR and CRP can evaluate the effect of drug level on ESR and CRP (Table 3). The current data exhibits a strong negative association between the Ixifi® trough level and ESR (r= -0.735) as well as CRP (r= -0.619) (Figure 5).

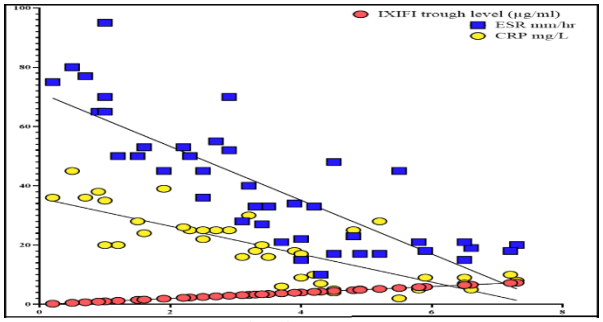

Figure 5: The correlation of Ixifi® trough level (TL) with ESR and CRP

This suggests that as the trough level increases, the levels of the biomarkers fall. On the other hand, the result shows a considerable positive correlation (0.755) between CRP and ESR in individuals diagnosed with rheumatoid arthritis (Table 3).

Table 3: Correlation between Trough level, ESR, and CRP biomarkers

Ixifi® TL (µg/mL)	Slop	r^2	p-value
ESR (mm/hr)	-9.071	0.672	0.0001
CRP (mg/L)	-4.720	0.638	0.0001

DISCUSSION

Ixifi® is biologically similar to Remicade®, which is the original or reference version of infliximab. Biosimilars are biologic medicines that closely resemble an original "reference" product and exhibit no clinically significant variations in terms of safety, purity, or potency when used to ameliorate the symptoms of RA [14]. According to this study, Ixifi® was able to establish remission in 38% of the participants in the sample. This proportion aligns with the findings of the study conducted by Koh *et al.* [15]. This study aims to further understand the correlation between Ixifi® TL and disease severity categories in individuals with RA. The examination of Ixifi® TL uncovered clear trends among different illness groups, providing insight into the possible usefulness of this biomarker in forecasting disease activity and treatment effectiveness. The variations seen in infliximab trough levels (TL) among RA patients with different levels of disease severity provide valuable insights into the development of the illness and the efficiency of treatment. The results of this study align with previous research [16,17], suggesting that greater levels of infliximab are linked to improved clinical outcomes. The notable differences in TL between remission and various disease severity groups emphasize the potential of these values as an indication of disease activity. The differences between the mild and moderate disease groups, as well as the moderate and severe illness groups, highlight the changes in infliximab response that occur with increasing disease severity, as mentioned in the research by Clair *et al.* [18]. This study investigated the potential of the erythrocyte sedimentation rate (ESR) to predict disease activity and treatment results in patients with RA. The average ESR readings exhibit a notable disparity within disease activity categories, as seen in Figure 3. These constant disparities imply that ESR has the capacity to evaluate the severity of the disease. This result is consistent with the study conducted by Fleischmann *et al.* [19] and also with the study conducted by Nair *et al.* [20] as well as in the study of Al-Hassan *et al.* [21]. On the other hand, this study aims to assess the correlation between CRP levels and disease activity as well as its potential as a predictor of treatment results. The mean concentration of CRP is assessed in several disease activity groups, revealing a considerable disparity among them, as seen in Figure 4. This finding validates the significant influence of CRP in evaluating the severity of RA. This conclusion is corroborated by the studies conducted by Tutan *et al.* [22] and Aletaha *et al.* [23], as well as by Thanoon *et al.* [24]. This study examined the associations between Ixifi® levels and key biomarkers, namely ESR and CRP. A negative regression slope, together with considerable R-squared values, demonstrates a robust and significant inverse connection between Infliximab TL and the levels of the important biomarkers. The results offer a valuable understanding of how Infliximab treatment affects changes in biomarkers related to disease activity and inflammation. Monitoring Ixifi® therapeutic levels has the ability to predict and evaluate therapy responses in individuals with rheumatoid arthritis (RA). The findings of this investigation are consistent with the results of recent studies [25–27].

Study limitations

This study has limitations, such as the relatively small sample size and the difficulty in getting the laboratory tests. Our suggestion is to take a larger sample size and include more than one center in the study.

Conclusion

A direct correlation exists between elevated levels of Ixifi® and a decrease in illness intensity, as well as

indicators of inflammation such as ESR and CRP. These findings suggest that a decrease in Ixifi® levels may contribute to the increase in disease severity and inflammation in rheumatoid arthritis patients.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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